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POTENTIAL PHARMACOLOGICAL ACTIVITIES OF FALOAK BARK (*STERCULIA QUADRIFIDA* R. Br.) AS AN HERBAL PLANT FROM EAST NUSA TENGGARA: A SCOPING REVIEW

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ABSTRACT
Faloak bark (*Sterculia quadrifida* R. Br.) is part of the faloak plant, which has been used for a long time in traditional medicine to treat a variety of medical conditions. Faloak bark is claimed to possess medicinal properties that can treat liver, kidney, and bladder diseases, cure gastroenteritis, hepatitis, anemia, malaria, back pain, and function as an energy booster. Recent studies in pharmacology have found that faloak bark has several interesting biological properties, thus strengthening its potential as a new source of active ingredients for pharmaceutical development. This study literature aims to provide a concise overview of the evaluations of the secondary metabolite chemicals found in faloak bark, thus highlighting their potential pharmacological properties. To find articles for the review of the pharmacological activities of faloak bark, a search was conducted on research journal databases using Publish or Perish 8, and 43 papers relevant to the evaluation were found. Literature review showed that faloak bark contains many different chemicals, such as alkaloids, gallic acid derivatives, flavonoids, polyphenols, saponins, steroids, tannins, terpenoids, triterpenoids, quinone, glycoside, as well as isolates of 2,3-dihydro-6-hydroxy-2-methylenenaphtho[1,2-b] furan-4,5-dione, and 2-iminoethyl 2-(1-hydroxypentan-2-yl) phenyl) acetate. Faloak bark has such pharmacological properties as antiaging, antibacterial, antibiofilm, anti-dengue, antifungal, anti-hepatitis C, anti-hyperglycemia, anticancer, antimalarial, antioxidant, antipyretic, and immunomodulatory effects. Therefore, faloak bark has considerable potential for the advancement of herbal remedies.

Keywords: pharmacology activity; secondary metabolism; *Sterculia quadrifida* R. Br.

1. INTRODUCTION

Indonesia has a rich heritage of traditional knowledge in utilising medicinal plants to address various health problems. Advantages such as easy access, low cost, self-preparation, and minimal side effects make medicinal plants remain relevant amidst modern technological advancements. Medicinal plants are also the subject of scientific research due to their potential for developing new drugs. Faloak (*Sterculia quadrifida* R. Br.) is an indigenous plant found in the Eastern Islands of East Nusa Tenggara, traditionally employed by the local community for the treatment of various health ailments associated with the liver, kidney, and bladder, energy booster, anemia, hepatitis, malaria, back pain, and gastroenteritis (Siswadi et al., 2021; Siswadi et al., 2015). It has been demonstrated that nearly all components of the root, seed, bark, and leaves show pharmacological activities, including antioxidant, cytotoxic, immunomodulatory,

antifungal, antiviral, antibacterial, antidiabetic, and antipyretic (Darojati et al., 2022; Dewajanthi et al., 2022; Rollando, Warsito, et al., 2020). The bark of the faloak plant possesses numerous health benefits and serves as a specimen for the research development of herbal medicine. Faloak bark contains secondary metabolites like alkaloids, terpenoids, flavonoids, phenolics, saponins and tannins, making it suitable for herbal medicine (Darojati et al., 2022; Dewajanthi et al., 2022). Thus, it provides a scientific basis for considering it as a potential source of herbal medicine. Although some studies have explored faloak bark, an integrated review of its pharmacological potential remains limited. Therefore, a comprehensive literature review is needed to highlight research progress and bridge the gap for innovation in developing herbal medicines based on faloak. This article aims to delve deeper into the pharmacological potential of faloak bark to provide a scientific foundation and future research directions for the development of natural product-based drugs.

2. METHODS

2.1. Data Collection Strategy

The articles used in this review were those published in the last 10 years. For this review, a reference search was conducted using the Publish or Perish 8 application with databases like Crossref, Google Scholar, PubMed, Scopus, Semantic Scholar, and SciFinder. Relevant articles were collected using several keywords, including "faloak bark", "*Sterculia quadrifida"*, "*kulit batang* faloak", and "*Sterculia quadrifida* R. Br." from national and international journal articles.

2.2. Selection Criteria

The inclusion criteria for the articles to be reviewed included articles written in Indonesian and English, written in full-text, published within the last 10 years (2014-2023), and reporting experimental studies related to investigating secondary metabolites and pharmacological activities of faloak bark. Meanwhile, the exclusion criteria included theses, dissertations, articles requiring full-text access, and articles discussing different species. Each obtained article was manually read to find those pertinent to the review topic. The search for journal articles yielded 43 relevant articles (**Figure 1**).

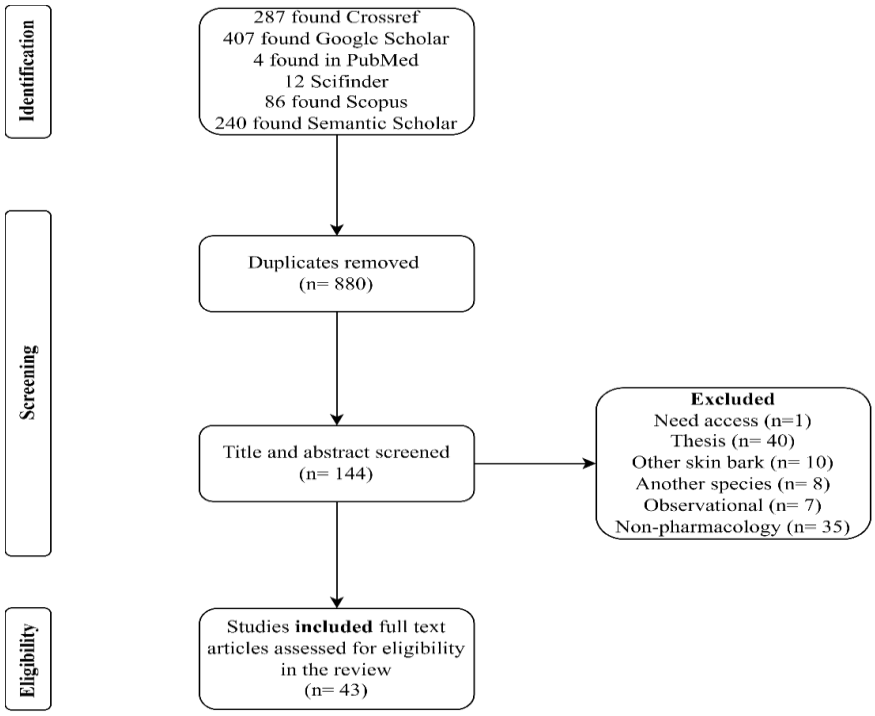

Figure 1. Diagram of Article Search Methodology

3. RESULTS AND DISCUSSION

Table 1 refers to the search's outcomes for relevant articles, with 43 articles discussing the pharmacological activities of faloak bark (*Sterculia quadrifida* R. Br.) to be reviewed. There were similarities and differences in the testing methods, subjects studied, and pharmacological activity tests. All the examined studies employed faloak bark samples for pharmacological activity testing and reported the findings of the tests conducted to detect chemical contents and pharmacological activities.

Faloak bark (*Sterculia quadrifida* R. Br.) has been the focus of research interest to discover potential medicinal properties for herbal drug development (**Figure 2**). The active compounds in faloak bark have shown pharmacological activities in addressing various health conditions, including infections induced by such microorganisms as bacteria, viruses, fungi, and parasites, as well as metabolic disorders and cell abnormalities. They also provide antipyretic effects, free radical scavenging, and immune responses.

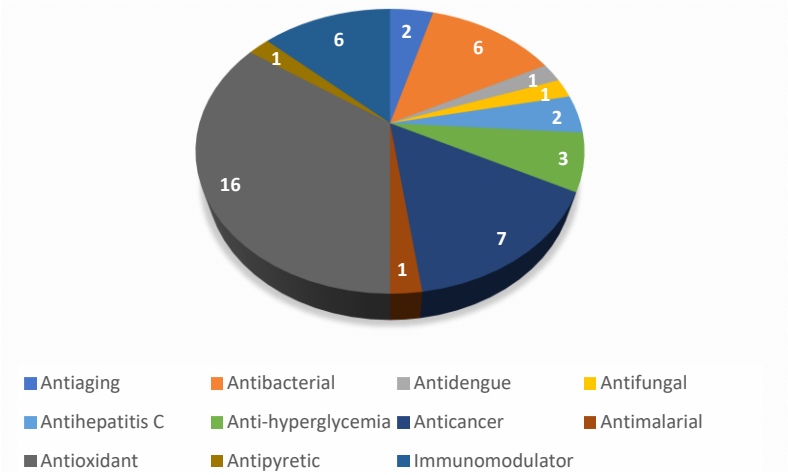

Figure 2. The Distribution of Research on Faloak Bark (*Sterculia quadrifida* R. Br.) from 2014 to 2023

3.1. Infections

The development of herbal medicine in the context of infections is often associated with efforts to discover or develop natural compounds that can help fight infections, with the hope of providing an alternative treatment and reducing the risk of increased antibiotic resistance. Faloak bark is one of the plants with the potential for an **antibacterial**. Its exhibited antibacterial activity macerated extract with 70% ethanol and ethyl acetate solvent, ethyl acetate fraction and kombucha which contains secondary metabolites, including flavonoids, phenols, saponins, alkaloids, steroids, and terpenoids, with their antibacterial properties against such bacteria as *B. subtilis*, *S. aureus*, *S. typhosa*, and *E. coli* (Lalong et al., 2023; Malik et al., 2023; Kapitan, 2018; Tenda et al., 2017; Rollando, 2015). When suppressing bacterial growth, **flavonoids** cause inhibition of cytoplasmic membrane function, resulting in significant potassium loss which therefore indicates direct damage to the cytoplasmic membrane of the bacterial cell wall. Additionally, flavonoids can prohibit important bacterial metabolism enzymes, such as RNA polymerase and DNA gyrase, thereby inhibiting nucleic acid synthesis. Flavonoids also disrupt nutrient exchange and metabolism, thus suppress energy supply (Xie et al., 2015). Meanwhile, **phenols** affect bacteria through damage to cell membrane walls, leading to changes in hydrophobicity and cell surface load, resulting in cytoplasmic leakage (Kauffmann & Castro, 2023). On the other hand, **saponins** are surfactants that make bacterial cell membranes less stable and more permeable, causing bacterial cell lysis and the release of proteins, nucleic acids, and nucleotides from bacterial cells (Khan et al., 2018). As antibacterials, **alkaloids** act as an inhibitor in DNA synthesis and block synthesis, disrupt cytoplasmic membrane integrity, cause oxidative stress that leads to cell cycle arrest and apoptosis thus

triggering cytoplasmic changes, and cause cell wall damage (Sulaiman et al., 2022). Additionally, **terpenoids** can inhibit growth by disrupting membrane and cell wall formation processes, resulting in incomplete or imperfect membrane or cell wall formation (Huang *et al*., 2022).

In addition, **biofilm** is a collection of microorganism cells, primarily bacteria, that adhere tightly to a surface accompanied by organic material and enclosed within an extracellular polymeric matrix produced by the bacteria. In a study by Rollando (2017), the methanol extract of faloak bark was fractionated by using n-hexane, ethyl acetate, and n-butanol. Silica gel was used as the stationary phase, while the mobile phase consisted of a mixture of n-hexane:ethyl acetate (100:0 to 0:100), followed by an isolation that produced three isolates of gallic acid derivatives with an anti-biofilm activity. **Gallic acid derivatives** belong to the group of phenolic compounds capable of inhibiting enzymes through nonspecific interaction with microbial proteins, breaking down bacterial proteins through the transpeptidase peptidoglycan activity that halts cell wall formation, and acting as an inhibitor of energy metabolism and nucleic acid synthesis in bacteria, thus possessing antibiofilm effects (Lobiuc et al., 2023). Antibacterial and antibiofilm study lacks identification of active compounds or isolates responsible for antibacterial activity. Further research should identify these compounds using methods like LC-MS or NMR, test against a wider range of bacteria, and compare results with positive controls, such as antibiotics.

The **dengue fever** disease or Dengue Hemorrhagic Fever (DHF) is caused by a virus transmitted through the bite of *Aedes aegypti* mosquitoes. It is essential to produce natural chemicals derived from plants that possess the ability to treat dengue virus infections. One of the plants that exhibits an anti-dengue activity is faloak bark (Riwu et al., 2022). The antiviral effect of **alkaloids** prevents the completion of the growth of viruses from various strains within infected cells. Alkaloids act as an antiviral by inhibiting replication through focusing cellular enzymes and process of protein synthesis. Some alkaloids have the ability to affect cells in two different ways simultaneously, which involve stopping both fusion and replication process. Additionally, some alkaloids show a distinct ability to interfere with the process of protein synthesis, particularly during the stage of peptide bond formation. Most studies confirm the inhibition of protein synthesis through the ribosome subunit RdRp (RNA-dependent RNA polymerase) 40S and some other specific virus receptors. Alkaloids induce alterations in nucleic acid sequences, leading to the suppression of vital message transfer for protein synthesis. Consequently, this restricts the production of the proteins required for viral infections (Abookleesh et al., 2022). **Flavonoids** such as **epicatechin** exhibit an anti-dengue activity by inhibiting the fusion of cell membrane and envelope proteins or inhibiting DENV2 (dengue virus 2) envelope proteins (Renantha et al., 2022). In addition, the estrogen receptor 1 on the NS1 (viral nonstructural proteins) is a potential target in a late-stage infection. The interaction between the receptors and the virus can weaken dengue fever productivity by disrupting virus translation and reducing virus proteins from moving to the cell surface (Hengphasatporn et al., 2021). The study is limited to *in silico* testing. Future research should include *in vivo* testing with animal models and *in vitro* testing using Huh-7 cells. Mechanism studies are also recommended to understand the compounds' action against the dengue virus.

Meanwhile, **hepatitis** is a disease caused by an RNA virus called HCV (hepatitis C virus). The faloak bark extracted with water, methanol, 70% ethanol, and fractions from the water extract have been tested and proved to possess a potential activity as an anti-HCV agent (Dean et al., 2019; Sola et al., 2018). Plants containing diverse varieties of active chemical constituents, such as **flavonoids** such as **epicatechin, terpenoids, polyphenols, saponins, alkaloids, coumarins,** a tendency to impede the replication process of various types of DNA or RNA viruses (Wahyuni et al., 2016). The test results of reduction steps in the HCV JFH1 life cycle revealed that the water extract of faloak bark showed an inhibition activity at the entry stage

where one of the interactions among the binding factors (glycosaminoglycans (GAGs) and Low-Density Lipoprotein Receptor (LDL-R)), receptors (Scavenger Receptor class B type I (SR-BI), CD81, Occludin, and Claudin 1), entry factors (EGFR, EphA2, TfR1, and Niemann-Pick C1-like 1 (NPC1L1)), and HCV JFH1 is inhibited, thereby inhibiting the JFH1 life cycle overall. In the post-entry stage, the water extract of faloak bark can suppress the NKT JFH1 life cycle through internal interactions, especially with the nonstructural parts involved in RNA replication, such as NS3 (Nonstructural protein 3), NS4B, NS3/NS4A, NS5A, and NS5B20 (Dean et al., 2019). This study has not isolated active compounds. Future research should focus on isolating and identifying active compounds using chromatography or mass spectrometry to understand their anti-hepatitis C activity.

Additionally, **fungal infections** can impact different parts of the body, including the skin, nails, oral cavity, digestive tract, or even internal organs. The development of herbal medicines in the context of antifungals involves the research and development of natural compounds from plants and herbs that have an antifungal activity. The extraction using a combination of methanol and water solvents produces the highest phenolic content, which correlates with the increased antifungal activity of faloak bark. **Phenolic** compounds act as an antifungal agent by destroying cell membranes, denaturing proteins, shrinking cell walls, and disrupting fungal metabolic pathways. Phenol is an oxygen hydrocarbon derivative with a potent antibacterial activity through interactions with fungal cells via hydrogen bonding processes. At small concentrations, phenol forms complexes with proteins through weak bonds that quickly degrade. Phenol can penetrate intracellularly, causing protein deposition and denaturation. Meanwhile, at high concentrations, phenol triggers protein coagulation and cell membrane lysis. Flavonoid compounds have an antifungal-properties by impeding fungal growth through the inhibition of nutrient diffusion processes, leading to fungal growth cessation or even death (Rollando et al., 2019). This study is limited to *Candida albicans*. Future studies should test antifungal activity against other clinically relevant species, such as *Aspergillus* spp., and compare them with standard drugs.

On the other hand, **malaria** remains an endemic health problem in Indonesia, especially in the eastern regions (Kemenkes RI, 2022). *Plasmodium falciparum* is the most lethal malaria parasite in humans and frequently encountered in Indonesia (Kemenkes RI, 2023). The antiplasmodial activity of 70% ethanol extract of faloak bark is closely related to the active compounds found in faloak bark that include alkaloids, flavonoids, and saponins (Tenda et al., 2021). The first isolated antimalarial drug belongs to the alkaloid compound group, which is quinine obtained from cinchona bark. Chloroquine, which is classified as a 4-aminoquinoline, was developed around the 1940s as a synthetic derivative of quinine. According to research by Rawe and McDonnell (2020), cinchona bark contains biologically-active **alkaloid** natural products, one of which is a quinoline derivative known as 4-Aminoquinolines (4-AQs) are employed for the treatment of malaria during the blood stage. The ability of 4-AQs to act as an antimalarial is present in the parasite's cytoplasm, impending the parasite's capacity to detoxify the heme by obstructing or restraining the creation of hemozoin. This causes the heme to interact with various parasite organelle membrane structures, including the digestive (or food) vacuole, leading to permanent damage and eventual parasite death. Additional studies have been conducted on *Artocarpus altilis* leaves, which produce a **flavonoid** isolate identified as 1-(2,4-dihydroxy phenyl)-3-[8-hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-2H-1-benzopyran-5-yl]-1-propanone with antimalarial potential. This compound resides in the parasite's food vacuole as a cysteine protease inhibitor, which inhibits the activity of the hemoglobinase II (plasmepsin II) enzyme, making hemoglobin unable to degrade into large fragments, and inhibits the activity of falcipain-2 enzyme, thereby impeding the degradation of large fragments into amino acids. Cysteine protease is an enzyme found in the food vacuole of *Plasmodium* parasites, which is crucial for hemoglobin breakdown, a procedure necessary for the erythrocytic stage of *P.*

falciparum to obtain amino acids. Hemoglobinase II (plasmepsin II) is an aspartic proteinase in *P. falciparum* participating in the breakdown of hemoglobin within the acidic food vacuole of the parasite's host cells. Falcipain-2 is a cysteine protease found in the food vacuole of *P. falciparum* participated in hemoglobin hydrolysis (Hidayati et al., 2020). Meanwhile, such **saponins** as glycyrrhizin demonstrate an antimalarial activity with the ability to penetrate membranes, thereby affecting the cell membrane integrity by damaging malaria parasite membranes thus causing leakage and cell death, and ability to inhibit the formation of fusion vesicles, leading to disruptions for parasite entry into cells and its metabolism (Soeiro et al., 2021). This study has not investigated fractions, isolates, or used other testing methods. Future research should include fractionation, isolation of active compounds, and testing against *in vitro Plasmodium falciparum* strain *3D7* and *in vivo*.

3.2. Antipyretic

An elevation of body temperature above normal, caused by the hypothalamus, is a sign of **fever**. Although fever is not a primary disease, it is a useful physiological mechanism to protect oneself from infections. The 96% ethanol extract of faloak bark positively contains flavonoids, steroids, terpenoids, and saponins showing a more optimal antipyretic activity compared to the positive control (Yuliani et al., 2016). The antipyretic activity of **flavonoids** is due to their capacity to inhibit the biosynthesis reaction of prostaglandins through the mechanism of cyclooxygenase 2 enzyme inhibition (Samiun et al., 2020). This study has not focused on fractions or isolates. Future research should perform fractionation and isolation to identify the main active compounds with antipyretic effects.

3.3. Metabolic Disorders

Metabolic disorders are a group of diseases associated with abnormalities in the metabolic processes of the body. Metabolic disorders can affect how the body processes carbohydrates, fats, proteins, or other substances and can lead to various health problems. **Hyperglycemia** is a medical disorder characterized by elevated levels of glucose in the bloodstream. Hyperglycemia is related to disruptions in the regulation of the insulin hormone, which plays a role in controlling blood glucose levels. Research on faloak bark macerated with 96% ethanol solvent and extracted using the decoction method with a water solvent and kombucha positively containing flavonoids, tannins, terpenoids, steroids, saponins, and phenols shows an activity in reducing blood glucose levels (Julianus et al., 2023; Lalong et al., 2022a; Fernandez & Edel, 2017). Another study has shown that **flavonoids** can inhibit the effect of α-amylase and α-glucosidase enzymes involved in the carbohydrates are broken down into monosaccharides that can be absorbed by the small intestine. If these enzymes are inhibited, carbohydrates will not be converted into monosaccharides and therefore cannot be absorbed by the intestines, thus preventing increased blood glucose levels. In addition, flavonoids play a role in inhibiting gluconeogenesis by inhibiting the transport of pyruvate into the mitochondria, increasing glucose uptake in tissues, stimulating insulin secretion from βcells, and protecting Langerhans degeneration (Ghorbani, 2017). Such flavonoids as apigenin, chrysin, fisetin, epicatechin, epigallocatechin gallate, genistein, luteolin, naringin, kaempferol, naringenin, puerarin, and quercetin can reduce blood glucose levels due to their antioxidant capability to protect and regenerate β-cells as an insulin producer and can enhance insulin sensitivity and secretion (Ghorbani et al., 2019). Meanwhile, **polyphenolic** compounds can enhance the insulin activity with an antioxidant activity and pancreatic regeneration as well as minimize the breakdown of polysaccharides and the absorption of sugars. Phenolics and flavonoids have an antioxidant activity and stimulate the action of superoxide dismutase (SOD) enzyme. Polyphenols can repair the pancreatic β-cells by reducing the development of cell toxicity through hydrogen atom donation (Chen et al., 2019). This study has not examined fractions or isolates. Future studies should perform fractionation to identify the most active anti-hyperglycemia fraction and isolate active compounds to explore their mechanism of action.

3.4. Free Radical Scavenging

Free radicals are molecules that possess one or more unpaired electrons and are highly reactive as they attack natural molecules in the body, such as unsaturated fatty acids, lipoproteins, proteins, and DNA. Oxidative damage to cells and tissues can occur due to the existence of free radicals in the body, which can contribute to various chronic diseases, including cancer, heart disease, and premature aging. Antioxidants are compounds that can combat or reduce oxidative damage by scavenging free radicals (Rollando & Monica, 2017).

Antioxidants can function by halting or reducing the chain reactions of free radicals in the body can lead to oxidative stress and cellular damage. Flavonoids, as a natural compound, possess the most potent antioxidant effects that can protect cells from oxidative damage. The faloak bark extracted with ethanol (70%, 80%, and 95%), ethyl acetate, and water as well as the antioxidant activity test of the water and ethanol fraction, instant powder, and kombucha show positive results of flavonoid, phenols, triterpenoids saponins, tannins, and alkaloids content (Riwu et al., 2023; Ruskim et al., 2023; Siswadi et al., 2023; Tenda et al., 2023; Lalong et al., 2022b; Maakh, 2021; Praing & Sunarni, 2020; Saragih & Siswadi, 2019; Soeharto & Tenda, 2019; Tenda et al., 2019; Hilaria & Tarigan, 2018; Tenda, 2018; Hertiani et al., 2017; Rollando & Monica, 2017; Amin et al., 2016; Rollando, 2015). **Flavonoids** possess the capacity to eliminate free radicals is based on their capacity to replace hydroxyl groups and stabilize phenolic radicals through hydrogen bonding or electron delocalization. In addition, the phenolic radicals of flavonoids are stabilized through delocalization of unpaired electrons around the aromatic ring. The resilience of flavonoid phenolic radicals (reactive oxygen species or ROS) will reduce the rate of autoxidation in chain reactions (Amin et al., 2016). Flavonoids, such as rutin and quercetin, act as an antioxidant against the damage lead by excessive ROS in sickle cell anemia. One of the enzymes responsible for the antioxidant activity is glutathione peroxidase (GPx), which is activated by flavonoid compounds (Praing & Sunarni, 2020). This study lacks isolation and identification of active compounds responsible for antioxidant activity. Future research should isolate these compounds and explore developing topical or oral dosage forms for clinical use.

Antioxidants can counteract ROS, making them suitable for use in **anti-aging** cosmetic products. Faloak bark extracted with 70% ethanol solvent and formulated into peel-off masks has proved to be the most effective in combating premature aging compared to the other parts of faloak, owing to its polyphenol, alkaloids, glycosides, tannins, terpenes, and flavonoid content that can combat ROS (Radjah et al., 2021; Khaeri & Nursamsiar, 2019). Antioxidants have a function in decreasing oxidative processes, hence lessening the detrimental impact of ROS in the human body, and stimulating collagen production as an anti-aging agent (Lourith et al., 2017). The antioxidant activity of **polyphenols** that have the ability to neutralize reactive oxygen species (ROS). Additionally, these compounds can improve the activity of Sodium Oxide Dismutase 1 (SOD1) in the cytosol and SOD2 in the mitochondrial matrix. SOD1 and SOD2 are enzymes that convert superoxide into hydrogen peroxide and oxygen, thereby protecting body cells from oxidative stress and potential DNA damage that can lead to premature aging (Luo et al., 2021). **Flavonoids** provide an antioxidant effect by reducing the levels of metalloproteinase-1 and carbonyl proteins while increasing the collagen and hyaluronic acid content, thus shielding against the elevation of the pro-inflammatory cytokines IL-1β and IL-6 (Alves et al., 2019). This study is limited by using only one extraction method is Ultrasound-Assisted Extraction (UAE) and not varying extract concentration in the peel-off gel mask. Future research should explore additional extraction methods, like Soxhlet or heating, and vary extract concentrations to find the optimal anti-aging effects.

3.5. Cell Abnormalities

Breast cancer is an oncological condition characterized by the uncontrolled proliferation of aberrant cells inside the breast tissue. The management of breast cancer may encompass a

range of approaches, such as surgical intervention, radiation, chemotherapy, and hormone treatment. The treatment plan will be tailored to the cancer type and stage as well as to individual health factors. Herbal medicine has garnered attention as an alternative or complementary treatment for breast cancer. Research on faloak bark includes extraction using a 96% ethanol and water solvent and further fractionation using ethyl acetate solvent, thus yielding such metabolites as **alkaloids**, **terpenoids**, **flavonoids**, **isolated derivatives of naphthoquinone compounds,** including **2,3-dihydro-6-hydroxy-2-methylenenaphtho[1,2-b] furan-4,5-dione,** and **2-iminoethyl 2-(1-hydroxypentan-2-yl) phenyl) acetate**, followed by activity testing against T47D cells. The research results show that the cytoskeleton is disrupted, the cell adhesion proteins do not polymerize, which indicates morphological changes as the cells do not bind to each other, and the lipid membrane rounding occurs. Decreased cell viability and density as well as morphological changes that leads to shrinkage are indicators of cell death. The anticancer mechanism of ethyl acetate fractions may occur through a p53-independent pathway in the S phase. The independent pathway of p53 status and the occurrence of S arrest (cell cycle arrest) are likely due to a rapid decrease in Cdc25A activity. When Cdc25A phosphatase is degraded, which depends on ATM-Chk2, it can inhibit CDK2 thus triggering cdc45 (the replication checkpoint), which slows down DNA replication. As a result, DNA replication ends, and S arrest occurs. The results show that the ethyl acetate fraction escalates apoptosis and modulates the cell cycle in the S phase. Modulation in the S phase or the occurrence of S arrest prevents cells from replicating, resulting in non-proliferating cells. The results indicate cell accumulation in the S and G2/M phases. Cell accumulation is caused by the arrest of the cell cycle in these phases. The S phase shows replication in preparation for the G2 phase, resulting in the number of chromosome set being between 2n and 4n, while the G2 phase produces 4n chromosomes (2 diploid cells) (Rollando et al., 2018; Rollando, 2018; Rollando & Prilianti, 2018; Rollando & Alfanaar, 2017; Rollando & Prilianti, 2017; Siswadi & Rollando, 2016). This study focused on breast cancer cells. Future research should include other cancer types, such as lung, liver, blood, or colon cancer, and perform *in vivo* testing to evaluate systemic effects.

3.6. Immune Response

Immunomodulators are agents that can modulate or regulate the role of the immune system of the body. The immune system is responsible for defending the body from infections, diseases, and abnormal cells, including cancer cells. Immunomodulators can work in various ways, such as increasing or decreasing the activity of the immune system, which depends on the health condition and needs of the body. The 80% ethanol extract, water extract, and ethyl acetate fractions of faloak bark tested positive for tannins, phenols, steroids, terpenoids, saponins, triterpenoids, quinones, and flavonoids have proved to possess an immunomodulatory activity (Rollando et al., 2020; Hertiani et al., 2019; Nitbani et al., 2019; Winanta et al., 2019; Munawaroh et al., 2018; Hertiani et al., 2017). **Tannins** can increase the level of leukocytes and decrease the synthesis of inflammatory proteins, including interleukin-2 (IL-2), tumor necrosis factor (TNF-α), and ROS (Behl et al., 2021). **Flavonoids** can influence both the innate and adaptive immune responses in the body. The innate immune response is associated to the ability of flavonoids to enhance the activity of natural killer (NK) cells by regulating activation receptors, to reduce the process of maturation and differentiation of dendritic cells (DCs) through the inhibition of surface co-stimulator endocytosis, molecules, and chemotaxis that contribute to T cell activation, to reduce the excessive production of Neutrophil Extracellular Traps (NETs) which can cause tissue damage, and to inhibit excessive neutrophil oxidative burst which can lead to oxidative stress and cellular damage. In addition, flavonoids can suppress the activation of M1 macrophages associated with proinflammation and modulate the transformation from M1 to M2 thus allowing macrophages to be triggered by IL-4 and/or IL-13 to support the production of IL-10 and TGF-β.5. Meanwhile, the role of flavonoids in adaptive

immune responses is shown through the proliferation of regulatory T cells (Tregs) in controlling the immune system by suppressing hyperactive immune responses and preventing the activation of other T cells, enhancing the activity of cytotoxic T lymphocytes (CTLs) by regulating diverse transcription factors, inflammatory cytokines, and signal transduction pathways, and inhibiting the activation or proliferation of helper T cells (Th cells). In addition, flavonoids can have positive effects by inhibiting B cells to help control excessive immune responses or autoimmune disorders, activating B cells to enhance immune responses to infections, or increasing antibody production to fight pathogens (Han et al., 2022). This study lacks isolation of active compounds responsible for immunomodulatory activity. Future research should isolate and identify these compounds.

1 **Tabel 1**. Studies of the Pharmacological Activities of Faloak Bark *(Sterculia quadrifida* R. Br.)

No.	Research	Results	Reference
	Antiaging		
1.	The macerate was transformed into a peel-off gel mask using different polyvinyl alcohol (PVA) film bases into 3 formulas (F1, F2, and F3) containing 0.5% extract. The formula is tested for physical stability under accelerated storage conditions (accelerate test) which includes organoleptic observations, homogeneity, pH measurement, viscosity, spreadability test, adhesion test, and drying speed test. The antioxidant effectiveness was tested on the stable formula using the DPPH (2,2-diphenyl-1-picrylhydrazyl) method.	The test results indicated that the most stable ethanol extract formula was formula 3 (F3) with a 12% PVA concentration and an antioxidant activity IC_{50} (Inhibition Concentration) of 17.04 µg/mL.	Khaeri & Nursamsiar, 2019
2.	The samples of leaves, roots, stems, and bark were subjected to Ultrasound-Assisted Extraction (UAE) using an ethanol solvent. The phytochemical screening, microscopic identification, and elastase inhibition activity tests were conducted following technique provided by Sigma-Aldrich protocol. The extracts with the highest elastase inhibition activity underwent testing for total flavonoid and polyphenol contents.	All the extracts contained alkaloids, flavonoids, glycosides, tannins, and terpenes. Elastase inhibitory activity assay on leaves, roots, and stems with IC_{50} values of 183.05, 166.30, and 141.70 µg/mL, with an IC_{50} value of quercetin of 29.14 µg/mL. The faloak bark extract had the highest elastase inhibition activity, with an IC_{50} of 73.70 µg/mL, and the highest amounts of flavonoids and polyphenols, with 28.75 mg/g and 45.25 mg/g of extract, showing that it could be used for anti-aging treatment.	Radjah et al., 2021
	Antibacterial		
3.	The extraction was performed using the soxhlet technique using methanol as solvent followed by fractionation and isolation using column chromatography. The fractionation process obtained 10 ethyl acetate fractions. Elucidation was conducted utilizing Nuclear Magnetic Resonance (NMR) and Liquid Chromatography-Mass Spectrometry (LC-MS) instruments. The microdilution method was employed to assess the biofilm inhibition activity against *Streptococcus mutans* on biofilms that had formed on microplates and were stained with 1% crystal violet.	The isolation process yielded 3 derivatives of gallic acid (isolates 1 from fraction 4, 2, and 3 from fraction 5). The biofilm formation inhibition assays on isolates 1, 2, and 3 showed a high biofilm inhibition activity with IC_{50} values of 46.87, 45.87, and 42.65 µg/mL.	Rollando, 2017
4.	The macerate was tested for its ability to identify things by its color changes and its ability to kill bacteria by using the diffusion method with cylinders and clear areas around the cylinders.	The ethanol extract was found to include flavonoids, alkaloids, steroids, terpenoids, and saponins. The concentrations (v/v) of 22.50%, 45%, 75%, and 100% were able to suppress the growth of *Staphylococcus aureus*, resulting in average inhibitory zone diameters of 1.33 cm; 1.66 cm; 1.90 cm; and 2.13 cm. The concentration that effectively inhibited the development of *S. aureus* bacteria was 100%.	Tenda et al., 2017
5.	Faloak bark ethanolic macerate was liquid-liquid fractionated to obtain ethyl acetate fractions and subjected to qualitative identification by observing color changes. The antibacterial testing was performed using the diffusion method, with the parameter measured was the diameter of the inhibition zone around the cylinder.	The results of the qualitative identification of ethyl acetate fraction from ethanol extract test were positive for flavonoids, alkaloids, and saponins. The activity against *Salmonella typhosa* was observed at a concentration of 75% (v/v), resulting in an inhibition zone area of 15 mm, while the concentrations of 25% and 50% (v/v) did not exhibit an	Kapitan, 2018

No.	Research	Results	Reference
		antibacterial activity.	
6.	Faloak bark ethanolic macerate was fractionated, and then the separation of active compounds from the ethyl acetate extract was performed using preparative Thin Layer Chromatography (TLC). The Folin-Ciocalteu was used to assess the total phenolic of each fraction. The antimicrobial activity testing was conducted utilizing the disc diffusion method (Kirby-Bauer Test).	Active fraction screening showed that fractions 1, 2, and 3 had better activity in inhibiting the growth of test bacteria than fractions 4 and 5. The highest phenolic content was found in fraction 2, at 34.16 ± 0.76 mg GAE/g (Gallic Acid Equivalent), followed by fractions 1 and 3 at 20.14 ± 0.87 and 18.97 ± 0.23 mg GAE/g. Fraction 3 exhibited a high antibacterial activity with IC_{50} values against *Bacillus subtilis* of 90.51 µg/mL, *Escherichia coli* of 80.12 µg/mL, *Staphylococcus aureus* of 77.87 µg/mL, and *Salmonella typhi* of 61.23 µg/mL. The Minimum Bactericidal Concentration (MBC) results indicated that 99.90% of bacteria were killed at a concentration of 500 µg/mL.	Rollando, 2015
7.	The kombucha of faloak bark 1.6% with varying sugar concentrations was fermented for 14 days and then subjected to total phenol testing using the Folin-Ciocalteu method. The antibacterial activity testing against the *Escherichia coli* ATCC 25922 bacterium was conducted using the well diffusion method.	Erythromycin has an inhibition zone value of 16.96 mm. The treatment with 12% sugar had the lowest pH value (2.91) while total titratable acids (1.19%), total sugars (7.33%) showed the highest values, a total phenol content of 420.15 mg/L GAE, and the potent antibacterial activity with inhibitory zone value of 14.03 mm, which suggested that it could be used to kill bacteria.	Lalong et al., 2023
8.	The macerate was tested for an antibacterial activity against the growth of *Salmonella typhi*.	The ethanol extracts at concentrations of 22.50%, 45%, 75%, and 100% demonstrated antibacterial effectiveness against the growth of *Salmonella typhi* with the most potent inhibition being observed at a concentration of 100%, resulting in an average inhibition zone of 17.22 mm, thus indicating moderate inhibitory strength, while chloramphenicol has a strong inhibitory power with a value of 27.90 mm	Malik et al., 2023
		Anti-dengue	
9.	The testing was carried out using all the ligands from the extract and protein preparations sourced from the PubChem and RSCB databases. The PyMOL, Lipinski's Rule of Five Pyrx, and Discovery Studio 2.0 methods were used to analyze and visualize the potential of extract compounds against the envelope and NS5 RdRp (RNA-dependent RNA polymerase).	The epicatechin and scopoletin showed low affinity bonds, several noncovalent interactions, and similarity in amino acid interaction locations compared to the reference control, ribavirin. The extract contained epicatechin and scopoletin, which were antiviral substances that worked against the dengue virus by targeting the envelope protein and NS5 RdRp in particular.	Riwu et al., 2022
		Antifungal	
10.	The extraction used the reflux method with seven different solvent combinations. The Folin-Ciocalteu was used to assess the total phenolic, and *Candida albicans* was used to test for an antifungal inhibition. The most optimal solvent combination was analyzed with 2 factor 2 level simplex lattice design method on Design Expert v.11 software.	The optimal combination formula of methanol (100%) and methanol:water (50%:50%) solvents resulted in an increase in extract yield of 3.81% and 3.83%, total phenol content of 123.94 ± 0.77 mg/g GAE and 142.22 ± 0.57 mg GAE/g. and antifungal activity at concentrations of 5000, 4000, 3000, 2000 µg/mL was 0.63 ± 0.06; 0.62 ± 0.03; 0.62 ± 0.03; 0.62 ± 0.03 and 0.67 ± 0.01; 0.63 ± 0.06; 0.58 ± 0.03; 0.58 ± 0.03.Ketoconazole 10% showed an inhibition zone	Rollando et al., 2019

No.	Research	Results	Reference
		diameter of 0.77 cm. The most optimal solvent composition was methanol:water of 0.44:0.56, 3.95% (w/w) extract, total phenol content of 120.20 mg GAE/g, and potential for inhibiting fungal growth of 0.67 cm.	
		Anti-hepatitis C	
11.	The extraction was performed using several different solvents with ultrasonic assisted extraction and using water with decocta method, and all the samples were tested for an anti-HCV (Hepatitis C virus) activity using Huh7it cells and the HCV JFH1a virus strain. The cytotoxicity was determined using the MTT analysis. The most active extract was then fractionated using column chromatography and tested for an anti-HCV activity and cytotoxicity with MTT.	The analytical findings indicated that water, ethanol, and methanol extracts exhibited an anti-HCV activity with IC_{50} values of 6.06 µg/mL; 9.44 µg/mL; and 10.39 µg/mL. However, the activity of hexane and dichloromethane extracts against HCV was relatively low, as indicated by IC_{50} values of 51.93 µg/mL and 179.31 µg/mL. The water extract showed the highest activity, resulting in seven fractions. Fractions 5 and 6 had the greatest level of activity with IC_{50} values of 7.60 µg/mL and 8.87 µg/mL. The cytotoxicity of these two active fractions was shown to be no-toxic, as indicated by CC_{50} (Cytotoxicity Concentration) values exceeding 1957.20 µg/mL and >2,000 µg/mL. The ethanol, methanol extract, water, fraction 5, and fraction 6 of the water extract exhibited promising anti-HCV properties.	Sola et al., 2018
12.	The extraction was conducted for compound detection using LC-MS/MS. The inhibition of the life cycle of HCV JFH1 and toxicity were assessed using Huh7it hepatocyte cells.	The water extract included epicatechin as the active compound, with a concentration of 875 mg/kg. The water extract exhibited inhibition against HCV genotype 2a strain JFH1 with an IC_{50} of 11.67 µg/mL and toxicity in Huh7it hepatocyte cells with a CC_{50} >1000 µg/mL. The activity of the water extract could inhibit various stages of HCV life cycle. The inhibition in the Huh7it hepatocyte cell line during the entry stage was 93.97%, at the post-entry stage the inhibition was 96.75%, and the combined entry and post-entry inhibition had a value of 100%. The water extract showed a potential antiviral activity against HCV JFH1.	Dean et al., 2019
		Anti-hyperglycemia	
13.	The macerate was identified for the chemical compounds. The anti-hyperglycemic activity was tested on glucose-induced mice. A positive control (metformin dose of 65 mg/kg BW), a negative control (1% Na CMC), and three test groups (extract doses of 150, 300, and 600 mg/kg BW) were used. The blood glucose levels were assessed at 30 minutes intervals for a duration of 2 hours.	The finding of the phytochemical screening indicated that the ethanol extract contained compounds from the groups of tannins, flavonoids, terpenoids, steroids, and saponins. Administering dosages of 150, 300, and 600 mg/kg BW resulted in reduced blood glucose levels. The difference in the highest reduction in blood glucose levels at 120-150 minutes was in the metformin positive control group at 71.40 mg/dL followed by the 150 mg dose of extract at 65.50 mg/dL.	Fernandez & Edel, 2017
14.	The experiment consisted of a normal control (rats kept under ordinary conditions), a negative control (DM rats), test group 1 (0.40% of black tea kombucha), test group 2 (1.60% of fermented faloak bark kombucha), and test group 3 (8g of faloak bark brew). The test samples were orally administered at a dose of 5 mL/kg	All test samples effectively reduced the fasting blood glucose levels, increased SOD, decreased MDA levels, lowering lipid profiles, increasing HDL levels, and repaired pancreatic β-cells within the islets of Langerhans. The antioxidant activity showed significant differences in the fermented faloak bark kombucha at 82.21% with the highest	Lalong et al., 2022a

No.	Research	Results	Reference
	BW/day for 28 days. The test used alloxan-induced diabetic rats. The analysis included fasting blood glucose levels, body weight, pancreatic histopathology, superoxide dismutase (SOD) activity, malondialdehyde (MDA) levels.	total flavonoid content at 4,134.78±97.54 mg/L QE (quercetin equivalent) and phenols at 467.92±8.37 mg/L GAE. The fermented faloak bark kombucha test group showed the most potent reduction in fasting blood glucose levels with a level of 120.80 mg/dL and showed more effective changes and a significant increase in the number of β cells compared to the faloak bark brew treatment.	
15.	The extraction was performed using the decoction method with water as the solvent. The *in vivo* testing was performed on male rats induced with the dosage of sucrose is 4 g/kg BW, with the normal control given distilled water, the positive control given acarbose (40 mg/kg BW), and the 3 test groups given the sample at doses of 0.8; 1.67; and 3.3 g/kg BW. The *in vitro* testing was performed at various doses utilizing the alpha-glucosidase enzyme reaction.	Administration of acarbose reduces glucose levels by 52.50% showed significantly lowering glucose levels. The water extract activity as an anti-hyperglycemic agent showed results at doses of 1.67 and 3.30 g/kg BW, reducing glucose levels by 62.20% and 56.90%, while a dose of 0.8 g/kg reduces glucose levels by 26.60%. Faloak bark decoction has activity as an α-glucosidase inhibitor of 42.09 ± 4.39%.	Julianus et al., 2023
		Anticancer	
16.	Faloak bark ethanolic macerate was fractionated using the preparative TLC method. The cytotoxicity testing against T47D and Vero cells was conducted using the MTT method, IC_{50}, and Selectivity Index (SI).	The study produced five fractions. Fraction 4 showed the most dominant at a moderate anticancer activity with an IC_{50} value of 21.89 µg/mL against T47D cancer cells with an SI value of 9.73, followed by fraction 3 of 53.34 µg/mL, fraction 2 of 78.98 µg/mL, fraction 1 of 121.76 µg/mL, and fraction 5 of 132.67 µg/mL	Siswadi & Rollando, 2016
17.	Faloak bark ethanolic macerate was separated into different fractions using n-hexane, ethyl acetate, and n-butanol. The ethyl acetate fraction was separated using column chromatography. Of the 10 fractions recovered, fraction 6 underwent further separation using column chromatography. The final separation yielded isolate 1. The structural analysis was performed using infrared spectroscopy, 1D-NMR, 2D-NMR, and MS. The isolate was evaluated for an anticancer activity against T47D breast cancer cells using the MTT method.	The isolation process resulted in a derivative isolate of the naphthoquinone compound, 2,3-dihydro-6-hydroxy-2-methylenenaphtho[1,2-b] furan-4,5-dione, with an IC_{50} value of 9.88 µg/mL inhibition of T47D breast cancer cells and an SI value of 30.23.	Rollando & Alfanaar, 2017
18.	Faloak bark ethanolic macerate was subjected to qualitative testing for alkaloid compound identification, followed by fractionation using n-hexana, methanol, ethanol, and ethyl acetate separation using column chromatography. The breast cancer cell line T47D and the normal Vero cell line were tested using the MTT method. The induction of apoptosis for ethyl acetate fraction and flow cytometry was used to detect changes in the cell cycle modulation.	The ethanol extract was tested positive for alkaloids. The ethyl acetate fraction had the potent cytotoxic effect with an half maximal effective concentration (EC_{50}) of 24.88 ±2.43 µg/mL and an SI of 15.15. Cytotoxicity tests for the methanol, ethanol, and n-hexane fractions respectively had EC_{50} values of 139.12±1.54, 182.42±4.72, and 220.13±1.23. The dominant ethyl acetate fraction increased the number of cells in the S phase by 27.43% in T47D breast cancer cells. Cisplatin showed cell death of 6.65% and the ethyl acetate fraction of 11.88%, thus showing the most dominant increase in cell death in early apoptosis.	Rollando & Prilianti, 2017
19.	The ethyl acetate fraction was fractionated using preparative TLC through three stages of purity testing, including identification using TLC with three different mobile phases of different polarity,	Fraction 2 produces a single point and the melting point examination results show that it has a melting distance of 0.69°C, which indicates that fraction 2 is relatively pure. The compound isolates 2-iminoethyl	Rollando et al., 2018

No.	Research	Results	Reference
	identification using two-dimensional TLC with 2 different mobile phases, and LC-MS analysis. The purest and most active fraction (referred to as the active isolation) was identified using the gradient isolation method with spray reagents, and structural clarification was performed using information from FTIR, LC-MS, H-NMR spectroscopy, C-NMR, and DEPT.The MTT technique was employed to conduct cytotoxicity tests on T47D breast cancer cells.	2-(1-hydroxypentan-2-yl) phenyl) acetate exhibited an IC_{50} value of 7.12 µg/mL against T47D breast cancer cells and an SI of 47.53.	
20.	*Hedyotis corymbosa* L. (HCOL) and faloak bark were macerated and the compounds were identified using TLC. The T47D cells were tested using the MTT method. The combinations were evaluated by determining the Combination Index (CI) and measuring cell viability. The combined impact of apoptosis induction and cell cycle modulation were observed using flow cytometry.	The chemical compound identification revealed that both the ethanol extracts contained alkaloids and terpenoids. Single cytotoxicity test result of HCoL showed the most dominant anticancer activity with an IC_{50} value of 1.24±1.26 µg/mL when compared with faloak of 2.69±0.54 µg/mL while cisplatin of 15.82±0.75 µM. The combination at a concentration ratio of 1/12, 1/6, and 1/3 IC_{50} produces a CI value of no more than 1.00, thus proving that the combination has a synergistic effect and shows a decrease in cell viability and changes in the morphology cells. The cytotoxicity test results of the combination (1/6 IC_{50}) showed CI values < 1 at concentrations of 0.21 µg/mL for *Hedyotis corymbosa* L. extract, 0.45 µg/mL for faloak bark extract, and 2.50 µM for cisplatin. The combination has a percentage of cell cycle distribution on the S phase was 27.73±0.97 % and the percentage of cell death was 17.81±1.89% (were capable of inducing apoptosis) higher than the single treatment. The ethanol extracts of *Hedyotis corymbosa* L. and faloak bark had the potential to be co-chemotherapy agents.	Rollando, 2018
21.	Faloak bark ethanolic macerate was separated into fractions using the liquid-liquid extraction method and identified using TLC. The combined effect of cisplatin and ethyl acetate fraction on increasing sensitivity in breast cancer cells was observed and confirmed by the induction of apoptosis and cell cycle modulation. The cytotoxicity of the compound was assessed on T47D cells using the MTT assay. This combination was tested by determining the CI and cell viability. The combined impact of apoptosis induction and cell cycle modulation were observed using flow cytometry.	The ethyl acetate fraction contained alkaloids and terpenoids. Single cytotoxicity test result of ethyl acetate fraction showed the better anticancer activity with an IC_{50} value of 14.35±0.54 µg/mL when compared with cisplatin of 15.82±0.75 µM. The combination at a concentration ratio of 1/12, 1/6, and 1/3 IC_{50} produces a CI value of less than 1.00, thus proving that the combination has a synergistic effect and shows a decrease in cell viability and changes in the morphology cells. The cytotoxicity test results of the combination (1/6 IC_{50}) showed CI values < 1 at concentrations of 6 µg/mL for the ethyl acetate fraction and 2.50 µM for cisplatin. The combination has a percentage of cell cycle distribution on the S phase was 29.98±0.97% and the percentage of cell death was 13.78±1.89% (were capable of inducing apoptosis) higher than the single treatment. The ethyl acetate fraction has the potential to be used as a chemotherapeutics agent in	Rollando & Prilianti, 2018

No.	Research	Results	Reference
		combination with cisplatin to enhance the effectiveness of breast cancer therapy.	
22.	The aqueous, ethanol, and ethanol: aqueous (1:1) macerates were analyzed colorimetrically to determine the total phenol using the Folin Ciocalteu and total flavonoid content. The cytotoxic potential was evaluated using Vero and HepG2 cells. The active extracts underwent fractionation testing on T47D, MCF7, HepG2, and Vero cells using the MTT method. The fractions tested included hexane, ethyl acetate, and water fractions.	The profile of each extract shows the presence of flavonoids in the form of flavanones and shows DPPH radical scavenging activity. The ethanol extract had the highest total flavonoid and phenol content at 11.89% ± 0.28% b/b (%NE) and 22.09% ± 0.71% (GAE). Extracts were selected based on cytotoxic activity against HepG2 cells and SI against Vero cells. The ethanol extract showed the most potent IC_{50} value against HepG2 cells of 44.40 µg/mL and the largest SI of 7.54. The ethyl acetate fraction exhibited the most potent action against T47D, HepG2, and MCF7 cells with IC_{50} values of 9.56; 3.24; and 7.62 µg/mL, and SI values against Vero cells of 2.01; 5.94; and 2.52. The ethyl acetate fraction had prominent cytotoxic results against T47D and MCF7 cells (compared to doxorubicin), but the SI was lower. The ethyl acetate fraction showed the greatest activity, indicating the potential as an herbal chemo preventive agent against cancer.	Hertiani et al., 2019
		Antimalarial	
23.	The macerate was identified for the compound content by observing the color changes and tested using a microscopic method for its activity in inhibiting the growth of *Plasmodium falciparum* strain FCR3.	The identification of the compound content revealed that the ethanol extract contained flavonoids, alkaloids, and saponins. Chloroquine has an IC_{50} value of 4.81 ± 0.10 µg/mL. The higher concentrations showed the greater growth inhibition, with an IC_{50} value of 42.40 ± 9.52 µg/mL, indicating a moderate *in vitro* activity.	Tenda et al., 2021
		Antioxidant	
24.	The macerate was tested for flavonoids by observing the color changes and conducting the DPPH assay at a wavelength of 516 nm.	A positive result for flavonoids was shown by the formation of an orange color. Both ethanol extract and vitamin C showed a potent antioxidant activity with IC_{50} values of 4.81 ppm and 3.49 ppm, with a weaker extract activity.	Amin et al., 2016
25.	The macerate was tested for the total phenol and flavonoid content as well as DPPH activity.	The ethanol extract contained 34.43% GAE total phenols and 1.55% QE total flavonoids and exhibited a DPPH assay value of 84.07 µg/mL, compared to vitamin C which showed 74.72 µg/mL, indicating its antioxidant potential.	Hertiani et al., 2017
26.	Faloak bark methanolic macerate was fractionated using the liquid-liquid extraction, first fractionation using wasbenzine and aqueous, then the aqueous fraction was extracted using ethyl acetate, followed by an identification of the total phenolics with the Folin-Ciocalteu reagent and DPPH assay.	The aqueous fraction of methanol extract contains phenolic compounds contained 6.97±0.17 mg GAE/g. The IC_{50} value obtained was 45.63±1.47 µg/mL, indicating a very strong antioxidant activity.	Rollando & Monica, 2017
27.	The percolate was made into effervescent powder with citric acid and tartaric acid at a ratio of F1 (10:10), F2 (30:10), F3 (10:30), and F4 (30:30) and then subjected to a DPPH assay.	The ethanol extracts from F1, F2, and F3 exhibited a strong antioxidant activity with IC_{50} values of 28.92±3.31, 59.83±10.92, and 99.36±55.18, while F4 showed a weak antioxidant activity with an IC_{50} value of	Hilaria & Tarigan, 2018

No.	Research	Results	Reference
		173.78±84.21.	
28.	Faloak bark is macerated using hot water was formulated into a syrup and then subjected to qualitative identification of active compounds and a DPPH assay.	Flavonoids and triterpenoids were detected in the sample, indicating a positive results. The water extract at concentrations of 25, 75, and 100% exhibited extremely low antioxidant activity with IC_{50} values of 1,370±34.39 ppm, 1,281.33±49.49 ppm, and 1,042±42.93 ppm.	Tenda, 2018
29.	Faloak bark ethanolic macerate was fractionated, and then the separation of active compounds was performed using preparative Thin Layer Chromatography (TLC). The Folin-Ciocalteu was used to assess the total phenolic of each fraction. The antioxidant activity was assessed using the peroxide and reduction methods.	The highest phenolic content was found in fraction 2, at 34.16 ± 0.76 mg GAE/g, followed by fraction 1 and fraction 3 at 20.14 ± 0.87 and 18.97 ± 0.23 mg GAE/g. The peroxide method antioxidant activity testing showed that fraction 2 exhibited the highest reduction activity at 87% followed by fraction 1 at 71%, compared to the positive control vitamin C at 93%. Additionally, the decrease reduction method showed vitamin C at 95% and fraction 2 at 91%, indicating that fraction 2 had the highest reduction activity. Hence, fraction 2 demonstrated the best antioxidant activity overall.	Rollando, 2015
30.	The extracts were obtained from the bark, including uncut bark, newly grown bark, old grown bark, root bark, leaves, and branch bark. The stem lines were classified into 3 categories, including bark that had never been peeled, old regrown stem bark (>6 months after debarking), and new regrown stem bark (<6 months after debarking). The samples were tested for the total flavonoid content can be determined using the aluminum chloride colorimetric method and the phenolic content using the Folin-Ciocalteu reagent and DPPH assay.	The highest flavonoid concentration was found in branch bark at 1.25±0.10 QE µg/mL, followed by root bark at 1.15±0.07 QE µg/mL. The highest total phenolic content was found in branch bark at 10.43±0.08 GAE µg/mL, followed by old grown bark at 9.77±0.21 GAE µg/mL. The ethanol extract of newly grown bark showed stronger antioxidant activity with an IC_{50} value of 2.51±0.03 µg/mL, followed by old grown bark at 3.43±0.12 µg/mL compared to vitamin C at 4.74±0.04 µg/mL.	Saragih & Siswadi, 2019
31.	The extract obtained using the decoction method was crystallized to create an instant beverage. A qualitative identification of the active compounds and a DPPH assay were conducted.	The qualitative identification of the aqueous extract showed a positive existence of flavonoids and triterpenoids. The antioxidant activity was very weak with an IC_{50} value of 2,307.77 ±58.20 ppm.	Soeharto & Tenda, 2019
32.	A mixture of dry powder from faloak bark and ginger powder was crystallized to obtain instant ginger-flavored faloak. A qualitative identification of flavonoids and triterpenoids was conducted by observing the color changes and the DPPH assay.	The qualitative identification showed a positive presence of flavonoids and triterpenoids. The antioxidant activity was very weak with an IC_{50} value ranging from 2,044.20±32.84 ppm.	Tenda et al., 2019
33.	The macerate underwent compound identification DPPH assay, and evaluation of glutathione peroxidase (GPx) activity assessed from the liver of rats induced with diabetes by using 180 mg/kg bw alloxan monohydrate suspended in NaCl 0.9%. Group I was the normal control group received 0.5% CMC-Na orally. Groups II-VI were induced with alloxan intraperitoneally. Group II as negative control was orally administered vehicle. Group III as positive control was orally administered glibenclamide at a dose of 0.45 mg/kg bw. Groups IV, V, and VI were orally treated extract in CMC-Na	The compound identification of the ethanol extract confirmed the presence of flavonoids, triterpenoids, saponins, tannins, and alkaloids. It exhibited a potent antioxidant activity with an IC_{50} value of 4.86±0.01 µg/mL and rutin 4.23 µg/mL. The GPx activity significant at doses of 65, 130, and 260 mg/kg BW increased the GPx activity in liver tissue with value 36.7±0.66; 50.87±1.90; and 56.10±0.94 U/mg tissue, compared to the glibenclamide 62.83±1.44 U/mg. Activity of faloak extract at dose of 300 mg was higher than two other doses Ethanol extract could be used a supplement, as an antioxidant therapy,	Praing & Sunarni, 2020

No.	Research	Results	Reference
	suspension at dose of 65, 130, and 260 mg/kg bw. At the end of the experimental period (15^{th} days).	and preventing diabetic complications due to lipid peroxidation and free radicals.	
34.	The percolate underwent compound identification, and a Self-Nanoemulsifying Drug Delivery System (SNEDDS) was prepared for the DPPH assay.	The most optimal formula was Virgin Coconut Oil (VCO): Tween 80: Polyethylene Glycol (PEG) 400 (1:6.65:0.35 mL) with an ethanol extract content of 7.14 mg. Extract and vitamin C exhibited a very potent antioxidant activity with IC_{50} values of 38.51±2.16 ppm and 5.02±0.63 PPM, SNEDDS exhibited a strong antioxidant activity with IC_{50} values of 70.18±4.89 ppm.	Maakh, 2021
35.	Faloak bark at 0.80%, 1.20%, 1.60%, and 2.00% (w/v)) and black tea was powdered to be placed in a tea bag and used to make fermented kombucha for 14 days. The total phenol and total flavonoid content were tested using the $AlCl_3$ assay, and a DPPH assay was conducted.	At a concentration of 1.60%, it has the highest total phenols and flavonoids of 467.92±8.37 mg/L GAE and 4,135.14±63.47 mg/L QE, while black tea is 475.13±3.82 mg/L GAE and 3,981.80±27.99 mg/L QE. The antioxidant activity with the optimal concentration at 1.60% (w/v) of 82.21%, this result is better than antioxidant activity black tea of 80.15%.	Lalong et al., 2022b
36.	The extraction was conducted utilizing the infusion method using aquades, followed by drying to obtain powder. The FTIR analysis was performed to identify the compound groups, determine (+)-catechin, and perform a DPPH assay.	The FTIR test showed seven different chemicals: an alcohol, a polyhydroxyl compound, an isothiocyanate, an aromatic compound, a ketone compound, a secondary alcohol, and aromatic phosphates. The findings indicated that the mean level of (+)-catechin was 7.79%, and the antioxidant activity was moderate with an IC_{50} value of 51.5 µg/mL, while ascorbic acid of 11.6 µg/mL strong category	Riwu et al., 2023
37.	Maceration with graded extraction (the results are called fractions) using the solvents n-hexane, ethyl acetate and ethanol. Identification of flavonoids and polyphenols using TLC. The antioxidant activity of the fraction was tested using TLC bioautography with ABTS (2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid) reagent. Separation of the active fraction using column chromatography. Subfractions of the active ethanol fraction (SFFE A) were tested for purity using 2-dimensional TLC and antioxidant activity using the ABTS method.	The ethanol fraction contains polyphenol and flavonoid compounds. The most active ethanol fraction with the separation results obtained 8 fractions with fractions 4 and 5 being the most active, separated further, obtaining 6 fractions with the most active ethanol fraction separated further until a subfraction of the active ethanol fraction (SFFE A) was obtained with impure results. The inhibition percentages of SFFE A at concentrations of 125, 250, and 500 ppm were 80.93%, 95.54%, and 96.69%, indicating a strong antioxidant activity.	Ruskim et al., 2023
38.	The formulations included F1 pure dry powder, F2 90% dry powder and dried stevia leaves, F3 90% dry powder and 10% dried ginger, F4 80% dry powder, dried stevia, and 10% dried ginger, F5 70% dry powder and dried mint leaves, and F6 60% dry powder, dried stevia, and dried mint, then packed in tea bags. The Folin-Ciocalteu was used to assess the total phenolic, the $AlCl_3$ method was used to find the total flavonoid content, and the DPPH activity was checked.	F5 had the highest total phenolic of 68.20 ± 0.95% GAE and F6 had the highest flavonoid content of 0.09±0.004% QE. The highest antioxidant capacity was 1,044.33±28.48 ppm Ascorbic Acid Equivalent (EAA) in F1, and the lowest was 801.81±9.46 ppm EAA in F6 while it had the most preferred taste. The composition of ginger, mint, and stevia had a lower antioxidant activity compared to pure *S. quadrifida*.	Siswadi et al., 2023
39.	Faloak bark and red ginger ethanolic macerate were identified compounds and formulated into syrups F1 (7.5 g of faloak bark extract) and F2 (2.7 g of faloak bark extract + 2 g of red ginger extract), and their antioxidant activity was assessed using the DPPH method.	The ethanolic extract presented triterpenoids, flavonoids, phenols, and tannins while the red ginger extract contained alkaloids, flavonoids, terpenoids, saponins, and tannins. F1 obtained an IC_{50} of 114.002 ± 0.174 ppm, while F2 with the addition of ginger showed an increase in antioxidant activity with an IC_{50} value of 107.888 ± 0.115 ppm. both	Tenda et al., 2023

No.	Research	Results	Reference
		falling into the moderate category	
		Antipyretic	
40.	The macerate was subjected to chemical identification by observing the color changes. The samples were tested on male white mice induced with the HB DPT vaccine at a dose of 0.0013 mL/20 g BW. The positive control group was given acetaminophen at a dose of 1.3 mg/20 g BW, the negative control group was given Na CMC, and the test groups were given ethanol extract at doses of 150 mg/kg; 300 mg/kg; and 600 mg/kg. The temperature was measured for 3 hours at 30-minute intervals.	The identification showed positive results for flavonoids, steroids, terpenoids, and saponins. The ethanol extract at doses of 150 mg/kg and 300 mg/kg exhibited an activity comparable to acetaminophen while the dose of 600 mg/kg showed a more effective antipyretic activity than acetaminophen.	Yuliani et al., 2016
		Immunomodulator	
41.	The macerate was analyzed for the total phenolic and flavonoid content, and the immunomodulatory activity was tested on mice macrophages and lymphocytes.	The ethanol extract contained 34.43% GAE total phenols and 1.55% QE total flavonoids. The SI of less than 2 on mice lymphocytes indicated no intended stimulation to demonstrate the effect of higher concentrations of the test sample. The ethanol extract enhanced the macrophage phagocytosis activity, which correlated with the tested concentrations, indicating its immunomodulatory potential.	Hertiani et al., 2017
42.	The macerate was partitioned to obtain the n-hexane fraction, the ethyl acetate fraction, the aqueous fraction, and the insoluble fraction. Identification using TLC and the total flavonoid content of the extract and fractions was determined using an $AlCl_3$ reagent. The extract and fractions were tested for their effect on the phagocytosis activity of peritoneal macrophages in Balb/c mice *in vitro* using the latex beads method.	The ethanol extract, n-hexane fraction, and ethyl acetate fraction were positive for steroids, terpenoids, and phenolics, while the ethyl acetate fraction and ethanol extract were positive for flavonoids. The total flavonoid content of the ethyl acetate fraction was 4.29±0.03 mg of quercetin/g fraction equivalents. The ethyl acetate fraction had the greatest total flavonoid content and macrophage phagocytosis capacity at a concentration of 250 µg/mL was 51.94±4.67%. This value exhibited a substantial disparity compared to the cell control (7.50±1.29%), negative control of 0.06% dimethyl sulfoxide (6.25±0.36%), and positive control of echinacea® extract syrup at 200 µg/mL (9.97±0.33%). There was a significant positive correlation between the total flavonoid content of the faloak extract and fractions and their macrophage phagocytosis capacity (Pearson correlation coefficient of 0.78).	Munawaroh et al., 2018
43.	The aqueous, ethanol, and ethanol:water (1:1) macerates were analyzed using the colorimetric methods to determine the total phenol content with the Folin Ciocalteu and the total flavonoid content. The immunomodulatory activity was evaluated by observing the impact on mice macrophages and lymphocytes utilizing the *in vitro* methods.	The profile of each extract shows the presence of flavonoids in the form of flavanones and shows DPPH radical scavenging activity. The ethanol extract had the highest total flavonoid and phenol content at 11.89% ± 0.28% w/w (% NE) and 22.09% ± 0.71% (% GAE). All the extracts greatly increased the macrophage phagocytosis compared to the control. Water extract at a dose of 1 mg/mL produced the highest Phagocytosis Index (PI= 145.72%±0.18%) and the percentage of activated macrophages (64.89%±7.31%), indicating that it could increase macrophage phagocytosis as indicated by the high PI value.	Hertiani et al., 2019

No.	Research	Results	Reference
		However, all the extracts showed SI values < 2, indicating no effects on lymphocyte proliferation. The extracts could stimulate the macrophage phagocytosis activity *in vitro*, positively correlating with the content of flavonoids and phenolic compounds.	
44.	The macerate was subjected to chemical compound identification. The normal control group received no extract, the positive control group was administered with dexamethasone at 0.54 mg/kg BW, test group 1 received faloak extract at 250 mg/kg BW, and test group 2 received dexamethasone at 0.54 mg/kg BW for 14 days followed by a dose of faloak extract at 250 mg/kg BW for the next 14 days. The treatments were administered orally for 28 days. The leukocyte and leukocyte differential counts were assessment was conducted on day 14 before immunization and on day 25 after vaccination.	The identification of the chemical compounds showed that the ethanol extract contained flavonoids, tannins, saponins, triterpenoids, quinones, and total phenol of 82.05 g. The ethanol extract demonstrated its potential as an immunomodulator in adult quails under immunosuppressive conditions by increasing the leukocytes, lymphocytes, heterophils, and monocytes.	Nitbani et al., 2019
45.	The extraction using the decoction method was subjected to immunomodulator testing through an *in vivo* study of Balb/c mice. The normal control group received no treatment, the three test groups were administered with the samples at doses of 7.5; 11.75; and 17.5 g/kg BW, and the positive control group received *Phyllanthus niruri Linn*. (PN) extract (Stimuno®) at 0.585 g/kg BW. All the mice were vaccinated with the hepatitis B vaccine on days 7 and 14. The *in vivo* analysis activities were conducted on day 19. The immunomodulator effect activity was expressed in the macrophage phagocytic capacity, nitric oxide production, phagocytic index, OD of lymphocyte proliferation, and IgG titer.	The macrophage phagocytic capacity and phagocytic index greatly increased, the nitric oxide production changed significantly, but no change in the OD of lymphocyte proliferation and production of IgG antibodies. The water extract could enhance the macrophage phagocytic activity but did not affect lymphocytes and therefore did not influence adaptive immune responses.	Winanta et al., 2019
46.	The extraction of faloak bark and *meniran* using the reflux method, then formulated into eight different formulas for organoleptic testing. *In vitro* tests were conducted to test the induction effect on TNF-α and NF-κB. The study included a normal control group that received no treatment, a positive control group using Stimuno, a negative control group, and a test treatment group.The treatments were administered orally to Balb/b mice (*Mus musculus* L.) for 21 days. The lymphoid organs were isolated to measure IL-1 and IL-6 levels, assessing macrophage activity was conducted using an ELISA kits and read the absorbance at a wavelength of 450 nm.	Each formula exhibited a sweet taste and a unique aroma derived from the extract. The combination syrup of *meniran* water extract and faloak bark water extract was able to modulate TNF-α and NF-κB and increase the macrophage capacity by 535.01±358.15%; 57.86±1.46%; and 98.45±0.23% based on the data analysis of 5 formulas with a *meniran* extract to faloak bark extract ratio of 0.25:0.75. Formula 5 showed superior macrophage capacity, as Stimuno was able to enhance macrophage phagocytosis by 92.43 ± 5.32%, making this formula the most effective in supporting immunomodulatory activity. The *in vitro* immunomodulator tests, evaluated across eight formulas optimized using the Simplex Lattice Design method with two factors and two levels, identified a new optimal formula. This formula, with a desirability value of 0.993 (close to 1), had a ratio of 0.96993:0.0300704 and predicted immunomodulatory test outcomes with TNF-α of 394.55 ± 81.67%, NF-κB of 131.68 ± 16.73%, and macrophage phagocytic capacity of 91.47 ± 12.62%.	Rollando et al., 2020

4. CONCLUSION

The literature analysis found that faloak bark (*Sterculia quadrifida* R. Br.) has been examined in several forms, including extracts, fractions, isolates, kombucha, SNEDDS, syrups, peel off mask, dry powder, and effervescent powders. The analysis of faloak bark has confirmed the presence of alkaloids, flavonoids, saponins, steroids, tannins, terpenoids, triterpenoids, quinones, phenols, glycosides, derivatives of gallic acid until specifically 2,3-dihydro-6-hydroxy-2-methylenenaphtho [1,2- b] furan-4,5-dione, and 2-iminoethyl 2-(1-hydroxypentan-2-yl) phenyl) acetate. Faloak bark contains secondary metabolite chemicals that contribute to its pharmacological properties, such as anti-aging, antibacterial, antibiofilm, antidengue, antifungal, anti-hepatitis C, anti-hyperglycemia, anticancer, antimalarial, antioxidant, antipyretic, and immunomodulatory actions. Faloak bark (*Sterculia quadrifida* R. Br.) shows promising potential, and further research and exploration are therefore necessary to contribute to the development of herbal medicine.

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6. CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this research.

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