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Mangosteen (*Garcinia mangostana*): Extraction, Purification, Bioactivities and Toxicities

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Abstract

Mangosteen (*Garcinia mangostana*) is a popular tropical fruit known as 'the queen of fruits' due to its delicious flavour. It comprises phytochemicals, flavonoids, and polyphenols such as xanthones, anthocyanins, and phenolic acids. The *G. mangostana* pericarp, seed, and flesh bioactive compounds have been shown to have anticancer, antitumor, wound healing, anti-inflammatory, antigenotoxic, antioxidative, antimicrobial, and antiviral properties. This review focuses on the bioactivity of *G. mangostana*, with the most common bioactive compound discovered being xanthone, which is frequently used in cosmetics, antimicrobials, antioxidants, and pharmaceutical research. Various extraction methods, both conventional and non-conventional, have been used in studies, depending on the goal of the research. This review concludes by using a computerised database search technique to discuss the extraction methods available and the properties of the bioactive compounds found in various parts of *G. mangostana*, including the pericarp, seed, and flesh.

1. Introduction

G. mangostana is one of the most popular tropical fruits, known as the 'queen of the fruits' due to its juicy white flesh that has a slightly acidic and sweet taste consumed by many people (Yang *et al.*, 2017). This *G. mangostana* belongs to the Family Clusiaceae and genus Garcinia. Garcinia is a genus of plants native to Asia and Africa, with over 300 species from which bioactive chemicals such as xanthones, flavonoids, triterpenoids, and benzophenones have been isolated and described. Although all fruits from Garcinia species are edible, *G. mangostana* has gotten the most recognition in the real economy. *G. mangostana* fruit is round, dark purple or reddish, and the trees mature at 6 to 25 meters. Fruit production usually takes ten years or more, with a yield of roughly 400 fruits per tree that increases with age (Gutierrez-Orozco & Failla, 2013). Since antiquity, *G. mangostana* has been grown in Java, Sumatra, Indochina, and the southern Philippines. In Indonesia, it is a common dooryard tree. In 1855, the *G. mangostana* fruit in English greenhouses and its culture were later brought to the Western Hemisphere, where it became established in various West Indian islands, most notably Jamaica. It was later created in Guatemala, Honduras, Panama, and Ecuador on the mainland. It is also possible to cultivate it in southern Florida. *G. mangostana* does not grow well outside the tropics and is only fresh in local markets. The fruit was banned from importation until 2007 in the United States due to fears of introducing the Asian fruit fly; imported *G. mangostana* must be irradiated first to remove the pest (Article, 2021). *G. mangostana* is a valuable plant since its parts can be used in medicine and food. Parts of the fruit, pericarps, and stems of *G. mangostana* plants have been frequently utilised, whereas *G. mangostana* leaves have not been commonly employed as ingredients in traditional medicine. However, *G. mangostana* leaves contain antibacterial chemicals. Flavonoids, tannins, alkaloids, and saponins are the four active components in *G. mangostana* leaves (Suhartati *et al.*, 2019a). Figure 1 summarises all the topics discussed in this review paper.

Every method that has been used has its limitations and weaknesses. In liquid chromatography, using organic solvents and other additives, which are rarely compatible with bio or biochemical tests, is one of its limitations. Gradient-based separations, in which the solvent composition changes dramatically, are particularly problematic. In this instance, evaporation is frequently the most effective technique to remove interferences. Volatile chemicals, on the other hand, may be lost. Another issue is quick separations, which often do not correspond to the period required for the bioassay. When combined with mass spectrometry, gas chromatography separation for volatile chemicals is unparalleled due to its efficiency and excellent detection sensitivity. Only a few biochemical systems can be employed (Weller, 2012).
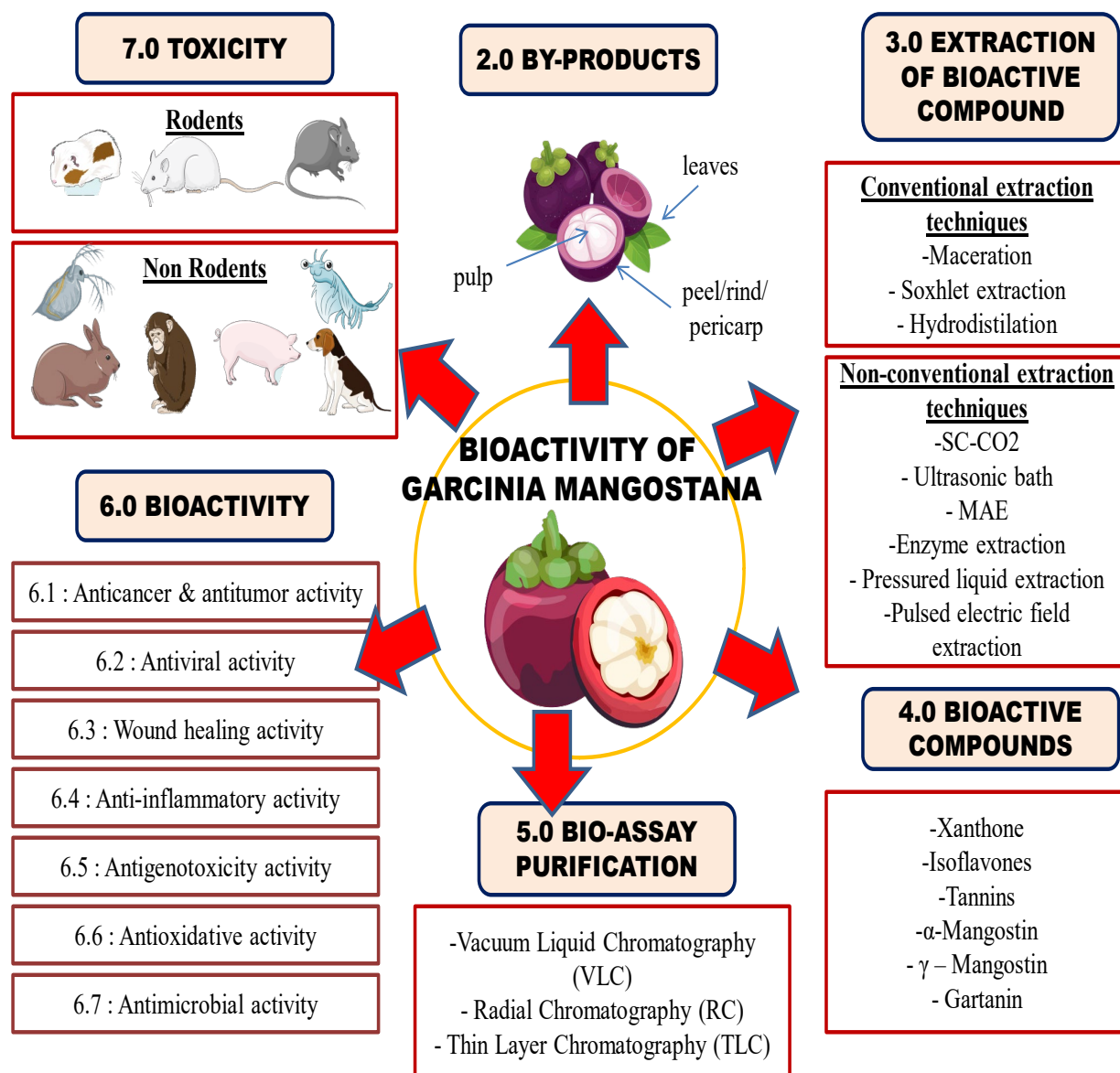
Figure 1: Bioactivity of *Garcinia mangostana*.

Parts of *G. mangostana* fruit, such as pericarps, pulps, stems, and leaves, are essential sources of bioactive components with various properties that will provide many benefits. Early descriptions of infusions and decoctions of its pericarps and seeds showed they were used to treat gastrointestinal and urinary tract infections. They were also used as anti-scorbutic, laxative, and anti-fever agents dating back nearly 200 years. In line with the rise of the times, *G. mangostana* is used modernly to treat infection-related symptoms like diarrhoea, stomach pain, and fever and complaints associated with inflammatory and immunological illnesses such as acne, food allergies and arthritis (Ovalle-Magallanes *et al.*, 2017). In Southeast Asia, the pericarp of the *G. mangostana* fruit has been used as a traditional medicine to treat infection, wounds and diarrhoea for ages (Gutierrez-Orozco & Failla, 2013). According to numerous in vitro and in vivo investigations, *G. mangostana* pericarp has a wide range of pharmacological actions, including antioxidant, anti-inflammatory, antibacterial, and anthelmintic due to its bioactive compound, xanthones (Markowicz *et al.*, 2019). Bioactive components in *G. mangostana* also have been found to have antiproliferative,

pro-apoptotic, antiobesity, anti-carcinogenic and antimicrobial activities (Gondokesumo *et al.*, 2019). The pericarp of *G. mangostana* is thought to contain medicinal characteristics, making it a possible natural therapeutic agent. It also can be used in various ways and be included in the diet to help fight infections (Datta *et al.*, 2014). Although there are many studies on the bioactivities of *Garcinia mangostana*, most of these studies have focused on common bioactivities such as antioxidant, antimicrobial, anti-inflammatory and wound healing. There is still a lack of up-to-date information on toxicity studies, antiallergy activity, and the anti-mutagenic activity of *G. mangostana*.

G. mangostana extract has been widely used since ancient times due to its several properties, which many researchers have proved in vitro and in vivo. On the other hand, the possible toxicity of extracts and formulations, including *G. mangostana* pericarps, pulps, and leaves, is still a minor worry as relevant data on toxicity are still lacking. Therefore, microbiological and toxicity tests must first determine their potential toxic effects. The goal of an acute toxicity test on *G. mangostana* pericarp

extract is to find out how dangerous it is and what the lethal dosages are (LD50). Dose levels are determined by preliminary information on symptoms, likely effects on target organs, and species sensitivity. The dangers of its usage or exposure to humans and a reference for designing additional safety and toxicity testing are calculated based on this outcome (Sunarjo, 2017). In addition, halal-related issues are also a significant concern when involving consumers among Muslims. Generally, Muslims are permitted to eat everything except those forbidden in the *Qur'an* or the *Hadith*. These *Shari'ah* (Islamic law) regulations provide people with the freedom to eat and drink whatever they like, as well as it is not haram (prohibited) (Khattak *et al.*, 2011).

This review paper evaluated the properties of the bioactive compounds found in various parts of *G. mangostana*, including the pericarp, seed, and flesh, and the available extraction methods used by a computerised database search technique.

2. *Garcinia mangostana* by-products

The *G. mangostana* tree grows to six to twenty-five meters, with lushes of thick leathery leaves covering the tree. Meanwhile, the fruit is round with thick skin, also known as pericarp and ripens seasonally, changing colours from green to yellow to pink spotted and full purple. The pericarp contains the edible part of the fruit, mainly composed of three to eight septa (also known as aril), which is white and has a sweet-sour taste. Its seeds are also found in one or two septa per fruit and are considered abrasive, cold-sensitive, and drying-resistant. This fruit's seeds often grow apomictically, without relying on sexual reproduction, and require a long planting period before bearing (usually 7 to 9 years), limiting the agronomic improvement and cross-breeding opportunities (Aizat *et al.*, 2019). Figure 2 shows the pericarps, pulps and leaves of the *G. mangostana*.
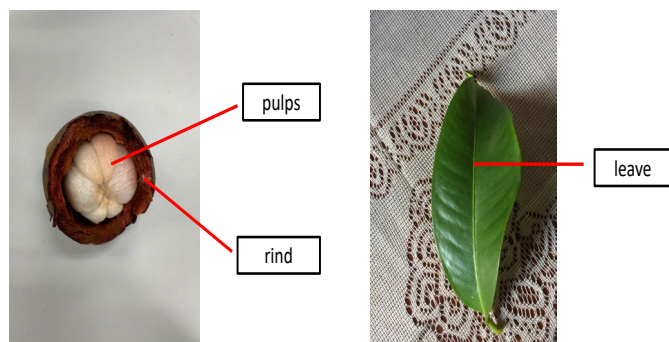

Figure 2: *Garcinia mangostana* pericarps, pulps, and leaves.

From 19 million tonnes of *G. mangostana* production in 2019 (FAOSTAT, 2019), 65% of the output, equalising 12 million tonnes, are the outer and inner pericarps (Chaovanalikit *et al.*, 2012). These underexplored by-products have gone to disposal, although they possess various bioactivities. According to Moopayak (2020), *G. mangostana* pericarp functions as an antioxidant, antitumoral, anticancer, antifungal, antibacterial, antiviral, antiallergy and anti-inflammatory agent. The seeds have antioxidant, antibiotic, and anticancer activities beneficial in pharmaceutical and cosmetic products. Both *G. mangostana* pericarp and seed have been used as bio-filters to produce natural rubber latex; for instance, medical gloves, rubber toys, rubber health care products and rubber transdermal patches. The antimicrobial properties of *G. mangostana* pericarp

protected the medical glove against undesired water and liquid molecule absorption and were effective against a virus (Moopayak, 2020).

In other studies, *G. mangostana* pericarp has been extracted into a gel and used for a patient with chronic periodontitis as additional therapy, which has improved clinical epithelium attachment in chronic periodontitis and reduced pocket depth and gingival inflammation after mechanical treatment such as scaling and root planing (Hendiani *et al.*, 2017). In food applications, the *G. mangostana* pericarp extract has also been used as anti-lipid oxidation in yoghurt drinks to hinder rancidity (Wibawanti *et al.*, 2019). All these bioactivity compounds act accordingly due to specific bioactive compounds in the *G. mangostana* by-products. Parts of the fruit, pericarps, and stems of *G. mangostana* plants have been commonly used, although *G. mangostana* leaves have not been widely used as ingredients in traditional medicine. However, *G. mangostana* leaves contain antibacterial compounds. *G. mangostana* leaf extract inhibits *E. coli* bacteria development, and the optimum concentration of *G. mangostana* leaf extract for inhibiting *E. coli* bacteria growth is 80% concentration with an average diameter of 32.75 mm (Suhartati *et al.*, 2019). *G. mangostana* seed contains several bioactive compounds, including oil, lipid, carbohydrate, moreollin and gambolic acid. *G. mangostana* pericarp contains xanthones which act as antibacterial and anti-inflammatory. The presence of xanthones in *G. mangostana* pericarp showed a higher radical scavenging activity. Flavonoids, tannins, alkaloids, and saponins are the four active compounds in *G. mangostana* leaves that render antibacterial potency.

3. Extraction of bioactive compounds of *Garcinia mangostana*

The extraction method is a process to separate the essential components from plant parts, such as antibacterial and antioxidant compounds. The characteristics of the compound to be extracted must be considered when choosing an extraction process. In a nutshell, extraction is one of the critical steps in creating medically beneficial extracts with the highest concentration of active constituents. The first prerequisite for producing an acceptable yield of active components in extracts is an appropriate extraction method and a suitable solvent. The attributes of the compound to be extracted must be considered when choosing an extraction process. The solvent and polarity index types, extraction times, solvent concentration and ratio, temperature, and particle size influence the extraction process's effectiveness and performance. The solvent and extraction time will have the most significant impact on the amount of extractable bioactive. When choosing a solvent for extraction, various factors must be considered, including availability, low cost, physical and chemical stability, neutral reaction, and potency to bioactive compounds (Kusmayadi *et al.*, 2018). Industrial legislation also mandates a reduction in petrochemical solvents and volatile organic compounds.

Furthermore, the lack of risk during extraction and the products' quality are significant concerns, prompting calls for greener solvents such as water and ethanol (Bundeesomchok *et al.*, 2016). Green extraction is a design of extraction procedures that can minimise energy consumption, allow for the use of alternative safe solvents and sustainable natural resources, and ensure a safe and high-quality extract. The polarity and concentration of the extraction solvents were essential factors in the extraction of α-mangostin from the *G. mangostana* pericarp. Various solvents, such as methanol, ethanol, and acetone, are widely used to remove secondary metabolites from

plant sources. The plant variety determines the type of organic solvent to use in the extraction process of the compounds to be extracted (Ghasemzadeh *et al.*, 2018).
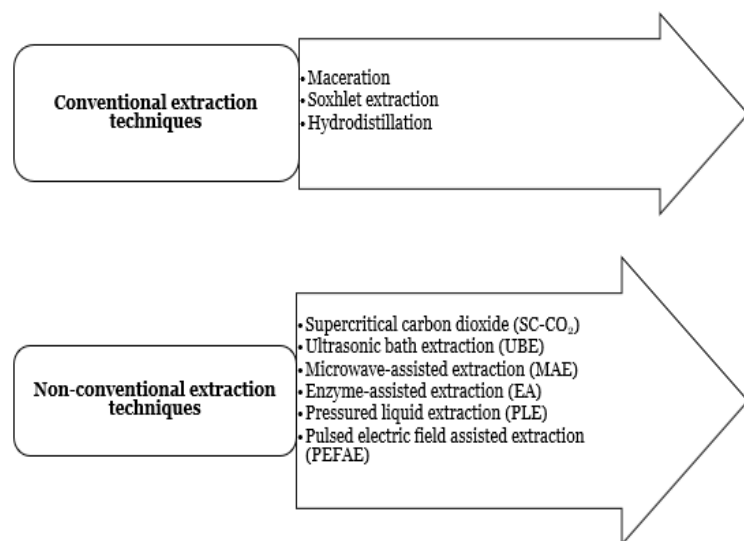

Figure 3: Type of extraction techniques.

Extraction techniques can be divided into two categories: conventional and non-conventional extraction techniques, as stated in Figure 3. Conventional extraction techniques include maceration in a water bath, soxhlet extraction (Mohammad *et al.*, 2019), and hydrodistillation (Azmir *et al.*, 2013). According to Ramesh *et al.* (2017), soxhlet extraction has been used to isolate Garcinone E from *G. mangostana* pericarp because it has been recognised to have a cytotoxic effect on the Sp2/0 cell lines. Sp2/0 cells are mouse-myeloma cell lines from B lymphocytes. They can be used as fusion partners for B cells to form hybridomas because they can develop indefinitely. On the other hand, conventional extraction techniques also have a few downsides, especially the maceration technique, which requires a high quantity of solvent and prolonged extraction time, especially during maceration in a water bath. Therefore, there has a variety of non-conventional techniques have been explored and can be used in the extraction of bioactive and phenolic compounds, such as ultrasonic-bath extraction (UBE) (Ahmad *et al.*, 2019), pressured-liquid extraction (PLE), microwave-assisted extraction (MAE) (Mohammad *et al.*, 2019), pulsed- electric-field-assisted extraction (PEFAE), enzymatic extraction (EA) and supercritical-carbon-dioxide extraction (SC-CO2) (Chhouk *et al.*, 2016).

Regarding Mohammad *et al.* (2019), the microwave-assisted extraction (MAE) method has been used to extract bioactive compounds, especially xanthones, from *G. mangostana* pericarp and analysed their total phenolic content and antioxidant activity. This method has been used for its superiority, such as less time consumption, little solvent consumption, and fast energy transfer, especially for preparing antioxidant-rich plant extract. The solvent is well diffused within the extraction medium during irradiation. However, potential influences on the extraction method include solvent types, volume, power, temperature, irradiation time, and raw material size. These variables impact the extracted yield and total phenolic content (TPC). The ultrasound-assisted extraction method was also used to compare its effectiveness with microwave-assisted extraction (MAE) in extracting bioactive compounds. These comparisons have been made because both techniques were used in previous studies (M'hiri

et al., 2015) to compare the different effects of different extraction conditions. Both methods can extract the highest amount of total phenolic content (TPC), making them the most common extraction methods over others, such as traditional solvent extraction (CSE), SC-CO2, and high-pressure extraction (HPE).

Other methods can also be used to extract bioactive compounds from *G. mangostana* pericarp, as Chhouk *et al.* (2016) used the supercritical carbon dioxide method in their study. On the other hand, supercritical carbon dioxide (SC-CO2) has been used in conjunction with subcritical water to overcome the disadvantages of the traditional process. The formation of carbonic acid lowers the pH of water when it is mixed with SC-CO2, particularly at high pressure. This makes the environment more conducive to extracting natural materials, usually attracted to acidic solvents. Using hydrothermal processes, SC-CO2 hydrolyse natural products like corn stover and hesperidin.

(a) α-mangostin

(b) mangostenone-F

(c) gartanin
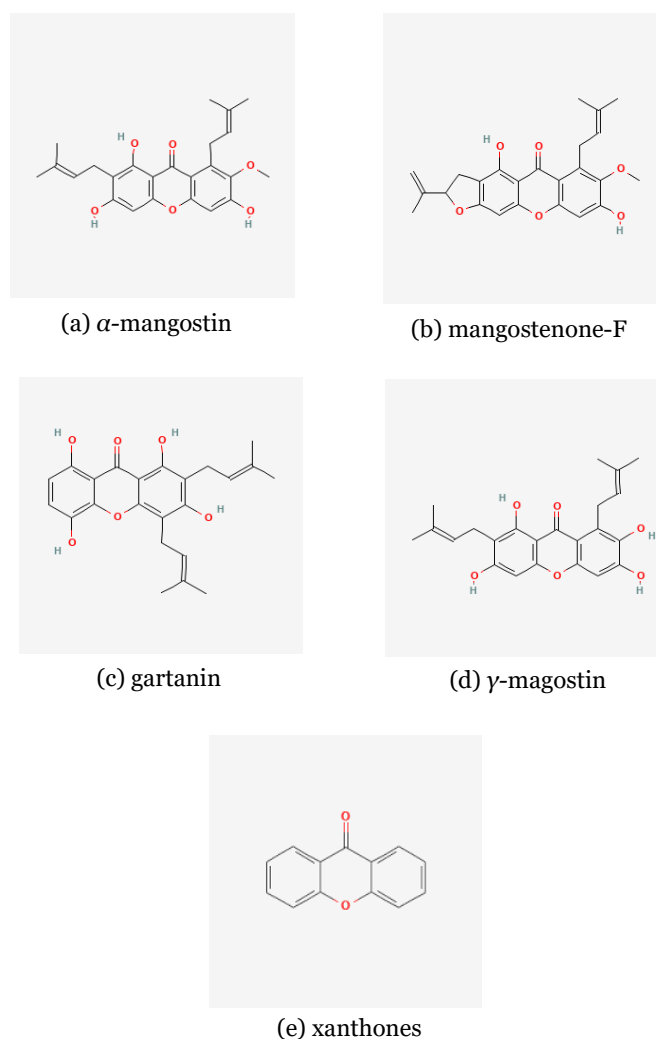

(d) γ-magostin

(e) xanthones

Figure 4: Chemical structure of active compounds in *Garcinia mangostana*.

4. Bioactivities and active compounds of *Garcinia mangostana*

Bioactive substances with medicinal qualities, including anti-inflammatory, antibacterial, anti-inflammatory, antitumoral,

antioxidant, HIV inhibitory, antilipidemic, wound healing and analgesic properties, are abundant and beneficial in the Garcinia species. These bioactivities are present due to the reported existence of polyisoprenylated benzophenones, flavonoids, and xanthones. Xanthones are chemical compounds found in *G. mangostana* pericarps that have antibacterial properties and can potentially halt cell multiplication in bacteria. *G. mangostana*'s major component, α-mangostin, has shown significant pharmacological effects, including antioxidant action in treating age-related macular degeneration and retinal protection against light damage (Espirito Santo *et al.*, 2020). Besides these active compounds, other compounds such as mangostenone-F, gartanin, γ-magostin, etc., in Figure 4 render specific bioactivities (Espirito Santo *et al.*, 2020), which will be discussed further in the following subtopics.

4.1 Anticancer and antitumor activities of *Garcinia mangostana*

Apart from antioxidant, anti-inflammatory, and antimicrobial activities, α-mangostin and xanthone of *G. mangostana* exhibit antitumor activity in vitro and in vivo studies. This is evident since it showed that it could inhibit cancer cell proliferation and metastasis and significantly reduce tumour growth through the induction of apoptosis and cell cycle arrest (Markowicz *et al.*, 2019). Metastasis occurs at first when the tumour cells separate from their original tissue. This calls for modifying both the cancer cell and the tissue of origin. Cancer cells in circulation must develop survival mechanisms after detaching (Patel *et al.*, 2011). The process of metastasis can occur when cancer can spread to other organs by invading any body area. Cancer is a condition brought on by a loss of control over cell growth brought on by cells that proliferate abnormally, spread, and grow beyond their normal boundaries (Guerrero-Pepinosa *et al.*, 2021).

According to Kurniawan *et al.* (2021), the type, number, and position of the connected functional groups in the xanthone framework determine the anticancer activity of xanthone derivatives. Multiple protein receptors, including cyclooxygenase, protein kinase, and topoisomerase, have been shown to bind with xanthone derivatives, indicating their anticancer action. Numerous xanthone derivatives for anticancer activities have been developed and tested. Anticancer agents based on simple oxygenated xanthones are being studied extensively. The anticancer effect of the 1, 3-dihydroxyxanthone against cancer cell lines is well recognised. Simple oxygenated xanthone showed potential anticancer action against the KB and MCF-7 cell lines via an antiproliferative mechanism among the produced xanthones. The anticancer activity of these xanthone derivatives was shown to be enhanced by nitrogen atoms in the heterocyclic rings. Since the intracellular enzyme may hydrolyse back to dihydroxyxanthone, the acetylated group increased anticancer action. Simple oxygenated xanthone showed substantial inhibitory activity against KB cells, with IC_{50} values of 2.40, 0.90, and 1.05 μM, respectively, while these compounds had IC_{50} values of 1.3, 0.8, and 0.9 μM against the MCF-7 cancer cell line. These were significantly lower than doxorubicin, with IC_{50} values of 25.0 and 25.7 μM for KB and MCF-7, respectively.

On the other side, panaxanthone (a combination of α-mangostin and γ-mangostin) was found to inhibit DNA replication and cause cancer cells to enter the G1 phase of the cell cycle. Subcutaneous injections of panaxanthone dramatically suppressed the metastatic growth of BJMC3879 cancer cells in mice. The inhibitory function was linked to the activation of caspase-3 and caspase-9 proteins, with the loss of cytochrome c from the mitochondria resulting in the collapse of cancer cells' mitochondria membrane potential. Subcutaneous injection of xanthone extract from *G. mangostana* fruit rinds containing 81% α-mangostin and 16% γ-mangostin dramatically reduced HCT-116 tumour volume in mice. The inhibitory action was linked to apoptosis induction, cancer cell motility, invasion, and clonogenicity suppression.

4.2 Wound healing activity of *Garcinia mangostana*

G. mangostana pericarp is traditionally used to treat sicknesses like wounds because it consists of many bioactive compounds such as xanthones, terpenes, anthocyanins, tannins, and phenols (Ovalle-Magallanes *et al.*, 2017; Shan *et al.*, 2011). Interference of cellular and anatomic continuity of tissue with or without microbial infection is the best term to define the wound meaning. Physical, chemical, thermal, immunological, and microbial exploitation causes the occurrence, which disrupts the epithelial tissue of the skin with the disturbance of functional continuity of living tissue in the wound (Shafy *et al.*, 2019). Cutaneous wound healing is a complicated and essential physiological process that relies on the interaction of cytokines, growth factors, chemokines, and chemical mediators from cells to carry out regulatory functions. Tissue regeneration and repair begin when an acute injury occurs, and any stimulation disrupts functional tissues' physical continuity. There have four stages in the wound healing process for acute wounds, including hemostasis, inflammation, proliferation and migration of the cells and tissue remodelling or resolution. Sometimes the coagulation and inflammatory processes are lumped together. The function and histological properties of these phases are unique. There is a logical path from injury to coagulation, inflammation, cell migration, and tissue remodelling in an acute wound (Freiesleben *et al.*, 2017; Sombolayuk *et al.*, 2019).

G. mangostana pericarp extract was reported to accelerate the wound healing process as its bioactive compound, such as xanthone. The most abundant xanthone presented in *G. mangostana* pericarp was known as α-mangostin, which was mainly mediated to give the wound healing effect. Coagulation, platelet aggregation, and fibrin clot formation are the first steps in inflammation. These mechanisms protect cellular materials from being lost, work as a physical barrier to prevent microbe access, and act as a provisional matrix, cytokine deposit, and growth factors necessary for the future healing phases to continue. Neutrophils are recruited within hours of injury and mediate tissue damage by releasing proteases, cytokines, and other substances housed in cytoplasmic granules. These cells produce reactive oxygen species (ROS) and antimicrobial proteases (cathepsins, defensins, lactoferrin, and lysozyme), which kill potentially harmful microbes. Neutrophils also have a variety of matrix metalloproteinases (MMPs) involved in the breakdown of the extracellular matrix. Uncontrolled neutrophil migration initiates a cycle of recruitment activation of these cells. This result produces excessive production of reactive oxygen species (ROS) and proteases, causing extracellular matrix (ECM) degradation and additional tissue damage, which may progress to chronic inflammation. This occurrence results in defective collagen deposition, reduced tissue resistance, late reepithelialisation and limited wound healing (Sombolayuk *et al.*, 2019).

Table 1: Wound healing graded score (Sombolayuk *et al.*, 2019)

Wound Healing Assessed	Graded Score (1-3)		
	1	2	3
Granulation tissue formation (GTF)	0-25% GTF with inflammatory cell domination	50-70% GTF with wide neovascularisation and less fibroblast	>75% GTF with domination of collagen and fibroblast
Reepithelialisation (RE)	No RE	RE<50%	RE>50%
Inflammatory cells count (ICC)	Mild macrophage and neutrophil	Moderate macrophage and neutrophil	Abundant macrophages and neutrophils

4.3 Anti-inflammatory activity of *Garcinia mangostana*

Inflammation is a vital part of the host's defensive system, including various activities in response to external stimuli such as pathogen infection, bacterial endotoxin exposure, and chemical exposure. Changes in blood flow, increased vascular permeability, tissue damage via activation and migration of leukocytes, and the creation of reactive oxygen derivatives (oxidative burst) and local inflammatory mediators, are all part of the inflammation process. Inflammatory mediators such as interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-, and Nitric Oxide (NO), as well as anti-inflammatory mediators such as IL-10, are secreted as a primary reaction to inflammation, in addition to leukocyte recruitment. Inflammation is linked to several disorders, including rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, Alzheimer's, and cancer. Anti-inflammatory is necessary to combat the risk of chronic inflammation that comes with chronic disease (Widowati *et al.*, 2016).

According to Tatiya-aphiradee *et al.* (2019), α-angostatin is the most prevalent xanthone in the *G. mangostana* pericarp. It has been shown to have antimicrobial and anti-inflammatory properties against various bacteria, including *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Propionibacterium acnes*. Using a tape stripping model, the anti-inflammatory activity of *G. mangostana* pericarp extract against methicillin-resistant *Staphylococcus aureus* (MRSA)-induced superficial skin infection in mice was examined. Topically administered *G. mangostana* pericarp ethanolic extract (GME) and its component, α-mangostin, to mice with MRSA-induced superficial skin infection. *Staphylococcus aureus* secretes the extracellular adherence protein in cutaneous infections, an anti-inflammatory agent to prevent leukocyte recruitment. Extracellular vesicles produced by *Staphylococcus aureus* trigger cytokine production and accelerated the inflammatory process, resulting in the formation of an abscess.

Several investigations have shown that *G. mangostana* and α-mangostin have been shown to have anti-inflammatory properties in cell cultures. *G. mangostana* extract (GME) and α-mangostin decreased the release of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) in RAW264.7 macrophage-like cells, while α-mangostin inhibited TNF- and IL-4. Furthermore, α-mangostin suppressed TNF-, IFN-, IL-6, IL-8, and IL-1 expression in human U397 macrophage-like cells and human primary adipocytes, as well as decreased levels of inflammatory cytokines such as TNF-, IL-4, and IL-8 in human enterocyte-like Caco-2, human colorectal adenocarcinoma (HT-29), macrophage-like THP. Interestingly, the study shows that *G. mangostana* extract (GME) and α-mangostin have anti-inflammatory effects in MRSA-induced superficial skin infection in mice by reducing the expression of pro-inflammatory cytokines such as TNF-, IL-6, and IL-1, as well as TLR-2.

4.4 Antigenotoxicity activity of *Garcinia mangostana*

Genotoxicity is known as the capacity of various chemicals to cause damage to genetic material. Moreover, the genetic material is damaged not only in terms of DNA but also in terms of cellular components that affect the operation and behaviour of chromosomes inside the cell. Proteins involved in the repair, condensation, and decondensation of DNA in chromosomes, or other structures responsible for chromosome distribution during cell division, such as the mitotic spindle, are examples. Genotoxic or genotoxins can cause genetic toxicity whereas antigenotoxicity is the inverse of this (López-Romero *et al.*, 2018).

According to Carvalho-Silva *et al.* (2016), the genotoxicity and antigenotoxicity of hydroethanolic *G. mangostana* extract (HEGM) were tested on *Saccharomyces* cerevisiae yeast. The antigenotoxicity activity of hydroethanolic *G. mangostana* extract (HEGM) was determined by comet assay using human peripheral blood cells (leukocytes). Pure α-mangostin extracted from the pericarp of *G. mangostana* was used to test for DNA antigenotoxicity. The finding was discovered that a concentration of 12.5 μM α-mangostin protected DNA from H2O2 damage in a dose-dependent manner. Cellular cytotoxicity was observed at higher dosages. As a result, the findings imply that some components in the pericarp of *G. mangostana* L., particularly α-mangostin, protect DNA against H2O2-induced damage. Cells were preloaded for 1 to 4 hours with HEGM (160, 320, 640 μg/mL), centrifuged, and washed twice with saline solution before being resuspended in RPMI 1640 medium and exposed for 5 minutes to H_2O_2 (1 mM) at 37°C. Alternately, cells were preloaded with α-mangostin 12.5 μg/mL for 1 to 4 hours, centrifuged, washed, and resuspended as before, but then exposed to H2O2 (1, 0.5, or 0.25 mM) at 37°C. The test revealed that it was effective against DNA damage caused by H_2O_2 in dosages up to 320 g/mL. (1, 2, and 4 hours exposure). When doubling the dose of HEGM from 160 to 320 μg/mL and comparing preloading up to 4 hours of exposure, it was discovered that improved DNA-induced damage protection was observed as a reduction in the quantity of identified DNA damage. Potential antioxidants in HEGM may protect cells by neutralising DNA damage-inducing H_2O_2-derived free radicals, preventing DNA-strand breaks identified by the Comet assay. Identifying compounds that can protect genetic material against genotoxic agents is critical because it indicates the ability to prevent diseases caused by genetic damage, such as cancer. Up to 640 μg/mL exposure concentration, the hydroethanolic extract of *G. mangostana* (HEGM) showed no genotoxicity/mutagenicity. Hence it was capable of preventing DNA against damage caused by free radicals produced by H_2O_2. Because of the lack of genotoxicity and the demonstrated antioxidant in vivo characteristics, extracts of *G. mangostana* are safe and even helpful to people since the incidence of oxidative stress-induced genetic damage may be reduced. *G. mangostana* extract, or isolated active components thereof, may offer promise for pharmaceutical or

nutraceutical applications by helping to prevent DNA damage-related disease by neutralising free radicals produced by cellular metabolism or external factors.

4.5 Antioxidative activity of *Garcinia mangostana*

An antioxidant compound in *G. mangostana* pericarp extract has been reported to be vital in promoting health benefits (Gondokesumo *et al.*, 2019). In the food industry, adding antioxidants is essential to inhibit the deterioration of food quality. Xanthones, prenylated and oxygenated xanthones, are the antioxidants in *G. mangostana* pericarp extract. Their various maturity levels of fruit skin affected the total bioactive compound content and antioxidant activities of Garcinia mangostana pericarps. The total flavonoid content has been found to be higher in the mature fruit pericarp (4.08g QE/100g) compared to the young fruit pericarp (2.91g QE/100 g) as it may result in higher antioxidant activity (Suttirak & Manurakchinakorn, 2014). Research also evaluated the antioxidant activity of *G. mangostana* pericarp can also be determined by their skin colour related to the concentration of phenolics and flavonoids (Lourith & Kanlayavattanakul, 2011). Compounds from the pericarp of *G. mangostana* were extracted using n-hexane, EtOH, and deionised water with different concentration ratios and periods of maceration. The most prolonged maceration period had the most *G. mangostana* colour, and the best solvent was water, followed by EtOH and n-hexane. Water and EtOH colour extracts were further examined for biological activity based on their colour preferences. The brilliant yellow EtOH extract had much higher antioxidant activity than the darker brown-yellow water-extracted colour. The proportion of phenolic and flavonoid components in the extracts, including xanthones, influences colour differences, although the EtOH colour extract's DPPH scavenging activity was 2-fold lower than the control. Furthermore, the EtOH extract had a higher total phenolic content but a lower flavonoid concentration than the other extracts. (Lourith & Kanlayavattanakul, 2011).

According to Palapol *et al.* (2009), the maturity levels of *G. mangostana* pericarp have been differentiated using Liquid chromatography-mass spectrometry (LC-MS/MS). The six different maturation levels of *G. mangostana* pericarp were classified based on their skin colour, as mentioned in Figure 5. However, the different maturity levels of *G. mangostana* fruit affected the bioactive compound content and antioxidant activity of the *Garcinia mangostana* pericarp extract due to the different xanthones concentrations (Pothitirat *et al.*, 2010; Suttirak & Manurakchinakorn, 2014). The xanthones concentration between each maturity level is different because of water loss of the fruit pericarp as their weight was reduced due to the ripeness process. The chlorophyll disappeared, and the carotenoid progressed, causing discolouration of the fruit pericarp from yellow, orange, red or purple during the maturation and ripening process (Gondokesumo *et al.*, 2019). Gartanin, γ-mangostin, smeathxanthone and garcinone-E are the standard compound present in all the maturity levels of *G. mangostana* pericarp extract, and the highest total of xanthones was reported in level 6 maturity of *G. mangostana* pericarp (Gondokesumo *et al.*, 2019). Antioxidant capacity was determined using electron spin resonance (ESR) analysis and 2,2-diphenyl-1-picrylhydrazyl (DPPH) as a free radical standard. The EPR spin trapping approach includes trapping reactive short-lived free radicals in a diamagnetic EPR passive compound (spin trap) via a spin trap double bond, resulting in a more stable radical product (spin adduct). According to the analysis, different stages of *G. mangostana* pericarp maturity have varying antioxidant activity, as seen by decreased free radical intensity. Compared to the DPPH free radical, each maturity stage of *G. mangostana* pericarp extract has a different g value. Different g values showed different types of free radicals while decreasing g values suggested decreased free radical intensity. *G. mangostana* pericarp, with maturity levels 4, 5, and 6, had the highest decrease in g value (Gondokesumo *et al.*, 2019).

Figure 5: Level of *Garcinia mangostana* and its characteristic. Source: (Gondokesumo *et al.*, 2019)

The ability of electron spin resonance (ESR) spectroscopy to discover antioxidative chemicals is well established. ESR spectroscopy is a one-of-a-kind approach for detecting free radicals and other compounds that do not affect the registered signal, and it reflects the researched material's actual antioxidative characteristics. The absorption of electromagnetic radiation was measured with an ESR spectrometer to detect antioxidant activity. The standard or stable free radical was DPPH (2,2-diphenyl-1-picrylhydrazyl), compared to DPPH plus six different maturity levels of *G. mangostana* pericarp extract. Compared to DPPH, the standard free radical, each maturity level has a different g value. The g value difference suggests a different sort of free radical. The antioxidant's ability to donate hydrogen atoms to trap the DPPH radical is measured by DPPH radical scavenging activity (DPPH). The structure, position, and degree of hydroxylation on the ring structure and the electron and hydrogen donating activity of polyphenols contained in *G. mangostana* pericarp extract all influence DPPH scavenging capacity. Maturation level is likely to impact the differences in antioxidant activity among the *G. mangostana* fruit. The flavonoid content of the mature fruit pericarp was higher than that of the young fruit pericarp. In conclusion, the higher total flavonoid content of the ripe fruit pericarp may explain its higher antioxidant action (Gondokesumo *et al.*, 2019).

4.6 Antimicrobial activity of *Garcinia mangostana*

G. mangostana extract has been proven through several studies to have antimicrobial abilities that are very effective in inhibiting the couples of gram-positive and gram-negative bacteria (Boonmak *et al.*, 2018; Panawes *et al.*, 2017; Soetikno *et al.*, 2016). The part that is often used to study its microbial activity is the pericarp part because it is always considered a waste product. However, it has many bioactive components that give many effective antibacterial effects (Datta *et al.*, 2014).

Referring to Saepudin *et al.* (2019), *G. mangostana* pericarp extract has been determined to have antibacterial activity against bacteria of the *Xanthomonas oryzae p.v. oryzae* (Xoo) that causes HDB disease (bacterial leaf blight) in rice and antibacterial components from the active extract has been identified. Bacterial leaf blight (HDB) is one of the most common rice diseases, affecting rice ecosystems worldwide. Pathogen Xoo infects rice plants during all stages of their development, from the nursery through the harvest. Xoo infects rice plants and degrades leaf chlorophyll by infecting portions of the leaves through leaf wounds or natural openings in the form of stomata. This infection reduces the ability of plants to carry out photosynthesis, resulting in death in immature plants and a less complete grain filling in generative phase plants.

Temperature and fruit storage duration substantially impact the antibacterial activity of *G. mangostana* pericarp extract. With an inhibition zone diameter of 24.46 mm and a minimum inhibitory concentration (MIC) value of 25%, *G. mangostana* fruit refrigerated for seven days at 13.5°C demonstrated the best antibacterial activity. Each treatment combination's inhibition zone of *G. mangostana* pericarp extract was higher than the chloramphenicol control inhibition zone. This result clearly shows that *G. mangostana* pericarp extract can prevent the growth of Gram-negative bacteria *Xanthomonas oryzae p.v. oryzae*. *G. mangostana* pericarp extract has a more substantial inhibitory effect than chloramphenicol antibiotics. Several active substances in the *G. mangostana* pericarp extracted with 95% ethanol, including xanthone, flavonoid, tannin, terpenoids, and saponins, determine this inhibitory effect. Xanthones are chemical compounds found in *G. mangostana* pericarp that have antibacterial properties and can potentially halt cell multiplication in bacteria. They are also high in antioxidants. Saponins work as antibacterials by interfering with the stability of bacteria's cell membranes, causing them to dissolve. The cell wall will be stretched severely, disrupting cell membranes, and releasing numerous essential components (proteins, nucleic acids, and nucleotides) required for bacterial life. Terpenoid is a lipophilic phenolic molecule. Terpenoids cause cell membrane damage as a mode of action. Tannin can stop protein transport enzymes from moving across cell membranes. Flavonoids are the most common type of phenol chemical with potent antiviral, antibacterial, and antifungal activities. Flavonoids tend to attach to proteins, causing metabolic disruption.

Regarding Li *et al.* (2020), natural compounds from *G. mangostana* pericarp have been identified to act as antibacterial action against *Ralstonia solanacearum* and thus find a way to employ this waste stream as a biological control for bacterial wilt. *Ralstonia solanacearum* causes bacterial wilt, one of agriculture's most severe bacterial diseases. Although chemical pesticides are used to prevent this illness, they may cause significant environmental pollution problems. Natural plant products can be a rich and environmentally compatible source of bacteria biological control across a broad spectrum. The pericarp of the *G. mangostana* was investigated utilising bioactivity-guided fraction analysis and liquid chromatography-mass spectrometry combined with multivariate analysis to identify markers of active fractions.

The antibacterial activity of six identified compounds (1; α-mangostin; 2, γ-mangostin; 3, smeathxanthone A; 4, mangostenol; 5, garcimangosxanthone H; 6, garcimangosxanthone I) was evaluated against *Ralstonia solanacearum*. Only γ-mangostin inhibited *Ralstonia solanacearum* growth in an agar medium, and α-mangostin had modest antibacterial activity, whereas the other compounds were inactive. In the OPLS-DA model, the VIP value of γ-mangostin (14.48) was the greatest, indicating that it was the most active compound in the active fractions.

4.7 Antiviral activity of *Garcinia mangostana*

Some studies show α-mangostin has antiviral properties as it can inhibit the production of dengue virus (DENV) in hepatocellular carcinoma HepG2 and Huh-7 cell lines and the expression of cytokine/chemokine in HepG2 cells. Dengue virus consists of four serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), and it was circulated and transmitted by *Aedes* mosquitoes and quickly passed the mosquito-borne disease to the human population (Quispe-Tintaya, 2017). As a broad spectrum of clinical phenotypes ranging from mild manifestation (dengue fever, DF) to the more severe spectrum (dengue hemorrhagic fever, DHF and dengue shock syndrome, DSS), DENV infection in a susceptible human host can be described as a capillary leakage, coagulopathy and organ impairment syndrome and partially thought to be immune-mediated.

Regarding Sugiyanto *et al.* (2019), α-mangostin has been reported to have the potential as antiviral as it is effective against dengue virus (DENV) infection in human peripheral blood mononuclear cells (PBMC) by determination of virus titer and tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) cytokines concentration after infection. TNF-α and IFN-γ were used to demonstrate the expression profiles of two cytokines involved in the inflammatory immune response to DENV infection and to identify the antiviral activity of α-mangostin. The cytokines/chemokines gene expression profiles were observed in patients during the dengue disease process. As a result, increased concentration of inhibited viral replication of α-mangostin and decreased production of inflammatory cytokines at 24 and 48 hours post-infection. The use of α-mangostin as an antiviral drug to inhibit the transmission of DENV is of valuable benefit, particularly in endemic countries where both circulating and secondary infections with DENV serotypes lead to a more severe form of the disease are inevitable. The intervention of α-mangostin in dengue patients during the acute phase of the disease can decrease the severity of the disease by raising the viral load and activating the immune response of the host by interfering with the function of the DENV NS5 protein necessary for the replication of DENV and reducing the transcriptional response of cytokines (Tarasuk *et al.*, 2017).

5. Bioassay-guided approach of *Garcinia mangostana*

Apart from investigating antibacterial, antifungal and antioxidant activities, the extract is also subjected to quantitative and qualitative phytochemical analysis. The composition of the crude extract of *G. mangostana* renders various bioactive compounds bound with impurities, where the

bioassay-guided approach on the crude extract separates. It purifies the bioactive compounds before further studies. Bioassay-guided approach fractionates components of crude extract based on differences in their physicochemical properties assessment of biological activity. Then, the fractionated components undergo another round of separation and assay to obtain a pure bioactive compound of natural origin, i.e. *G. mangostana* (Malviya & Malviya, 2017).

For this bioassay-guided approach, Vacuum Liquid Chromatography (VLC) incorporated with Radial Chromatography (RC) is the common technique to separate and purify secondary metabolites (Gartanin compounds) from *G. mangostana* pericarp. Both VLC and RC employ physical separation techniques where the fractionation of components of crude extract occurs between the mobile and stationary phases (Oetari *et al.*, 2019). In the chromatography principle, molecules in a mixture are placed on the stationary face's surface, and the mobile phase is injected to pass the mixture to be separated onto the solid phase. The essential factors effective in this separation process are molecular properties associated with adsorption (liquid-solid), partition (liquid-solid), and affinity or variations among their molecular weights. As a result of these discrepancies, certain components in the mixture spend a long time in the stationary phase and travel slowly through the chromatographic system, whereas others exit the system quickly (Sayed, 2021). Figure 6 shows the method to obtain the gartanin. To obtain pure gartanin compound from *G. mangostana* pericarp, the crude extract of *G. mangostana* undergoes fractionation via VLC to produce subfraction, followed by RC to obtain subfraction, which is anticipated to be a purified gartanin. To confirm obtaining the purified gartanin, the subfraction is subjected to Thin Layer Chromatography (TLC) to produce a single stain with a representative retention factor (RF). Meepagala & Schrader (2018) utilised silica gel to obtain and mark the stain with a fluorescent indicator. Subfractions of the *G. mangostana* with similar RF are combined, and the pure gartanin is subjected to confirmatory techniques such as spectrophotometry and mass spectrometry (Sani *et al.*, 2021).

In other studies by Meepagala & Schrader (2018), the bioassay-guided approach has been used to isolate and identify α-mangostin, γ-mangostin and (-)-epicatechin from *G. mangostana* pericarp extracted by ethyl acetate (EA) and methanol (ME) against the bacterium *Flavobacterium columnare* to help catfish aquaculture industry. Column chromatography fractions and purified compounds were analysed using silica gel thin-layer chromatography plates with fluorescent indicators. The step used is quite the same compared to (Oetari *et al.*, 2019). An isolated compound has been used to test the antibacterial assay against *F.columnare*. Isolation and identification of further fractionation of ethyl acetate and methanol extract, α-mangostin, γ-mangostin and (-)-epicatechin has been carried out via spectroscopic techniques. (-)-epicatechin showed the lowest activity while γ-mangostin showed the most significant activity compared to other purified compounds though α-mangostin is the major xanthone constituent in *G. mangostana* pericarp.

6. Bioactive compounds of *Garcinia mangostana*

Xanthone, tannins and flavonoids (isoflavones) are bioactive compounds found in *G. mangostana* pericarp extract. Xanthone is a group of yellow pigments and has been seen as the main polyphenolic compound in the *G. mangostana* pericarp. They are primarily polar compounds and can be dissolved in organic or hot water (Chhouk *et al.*, 2016; Pratiwi

et al., 2017). More than 50 xanthone derivatives were isolated from the pericarp of *G. mangostana*. However, from the xanthones that have been identified, α-, β-, γ-mangostins, garcinone E, 8-deoxygartanin, and gartanin are the most investigated (Ramesh *et al.*, 2017).

G. mangostana pericarp extract contains numerous bioactive chemicals, including prenylated and oxygenated xanthones and xanthones. The chemical structure of xanthones is unique, consisting of a tricyclic system (C6-C3-C6). The xanthones α and γ-mangostin are the most plentiful in *G. mangostana* pericarp. Garcinones C, D, 8-deoxygartanin, mangostin, garcinones A, B and E, mangostinone, 9-hydroxycalabaxanthone, and isomangostin are among the other xanthones found in *G. mangostana* pericarp (Gondokesumo *et al.*, 2019). Garcinone E has a significant cytotoxic impact against hepatocellular carcinoma and lung cancer cell lines. Garcinone E has an antiproliferative effect on gastric cancer cell lines and has been discovered to have a wide range of dose- and time-dependent cytotoxic effects on various cancer cell lines (Ramesh *et al.*, 2017).

The concentration of α-mangostin, the main xanthone, is substantially associated with most *G. mangostana*'s biological activities. Alpha mangostin has been isolated from dried *G. mangostana* extract and has been confirmed to have a wide range of functional properties, including antioxidant, antitumor, anti-inflammatory, antiallergy, antibacterial, antifungal, anticancer, antivirus and cytotoxicity activities (Chhouk *et al.*, 2016; Ghasemzadeh *et al.*, 2018).

G. mangostana pericarp extract is very popular in ancient medicine to treat abdominal pain, diarrhoea, infection and chronic ulcers. Thin Layer Chromatography (TLC) and High-Performance Thin Layer Chromatography (HTLC) are two modern techniques used to trace the quantitative analysis possible and determine α-Mangostin in *G. mangostana* pericarp. The TLC method was precise and exact (Pratiwi *et al.*, 2017). Based on (Muchtaridi *et al.*, 2017), α-Mangostin, γ-Mangostin, gartanin and 3-isomangostin can be isolated from *G. mangostana* pericarp extract. These isolated xanthones can provide various functions, especially for pharmacological uses, including antimicrobial, antimalarial, antioxidant, and anti-inflammatory. Many methods can be used to analyse the presence of bioactive compounds. High-Performance Liquid Chromatography (HPLC) validly analyses bioactive compounds such as α-mangostin, γ-mangostin and gartanin in *G. mangostana* pericarp extract. *G. mangostana* was purchased from different places in West Java, Indonesia (Bogor, Purwakarta, Tasikmalaya and Subang). The highest among other samples was the α-mangostin, γ-mangostin, and gartanin levels of *G. mangostana* pericarp from Bogor.

In addition, anthocyanin is also one of the bioactive compounds found in the *G. mangostana* fruit. Anthocyanin is a water-soluble flavonoid pigment in many flowers, fruits, and vegetables responsible for reddish, bluish, and purple hues. Anthocyanins have sparked a surge of interest in natural colourants because of their wide variety of colours and the many health benefits they have been linked to, including anti-inflammatory, antimicrobial, anti-carcinogenic, and anti-diabetic properties. Data suggests that anthocyanins are beneficial therapeutically and are also non-toxic and non-mutagenic. However, anthocyanin is highly unstable and quickly degraded in its isolated form, and its stability is greatly influenced by factors such as pH, temperature, oxygen, and light (Ramasamy *et al.*, 2016).
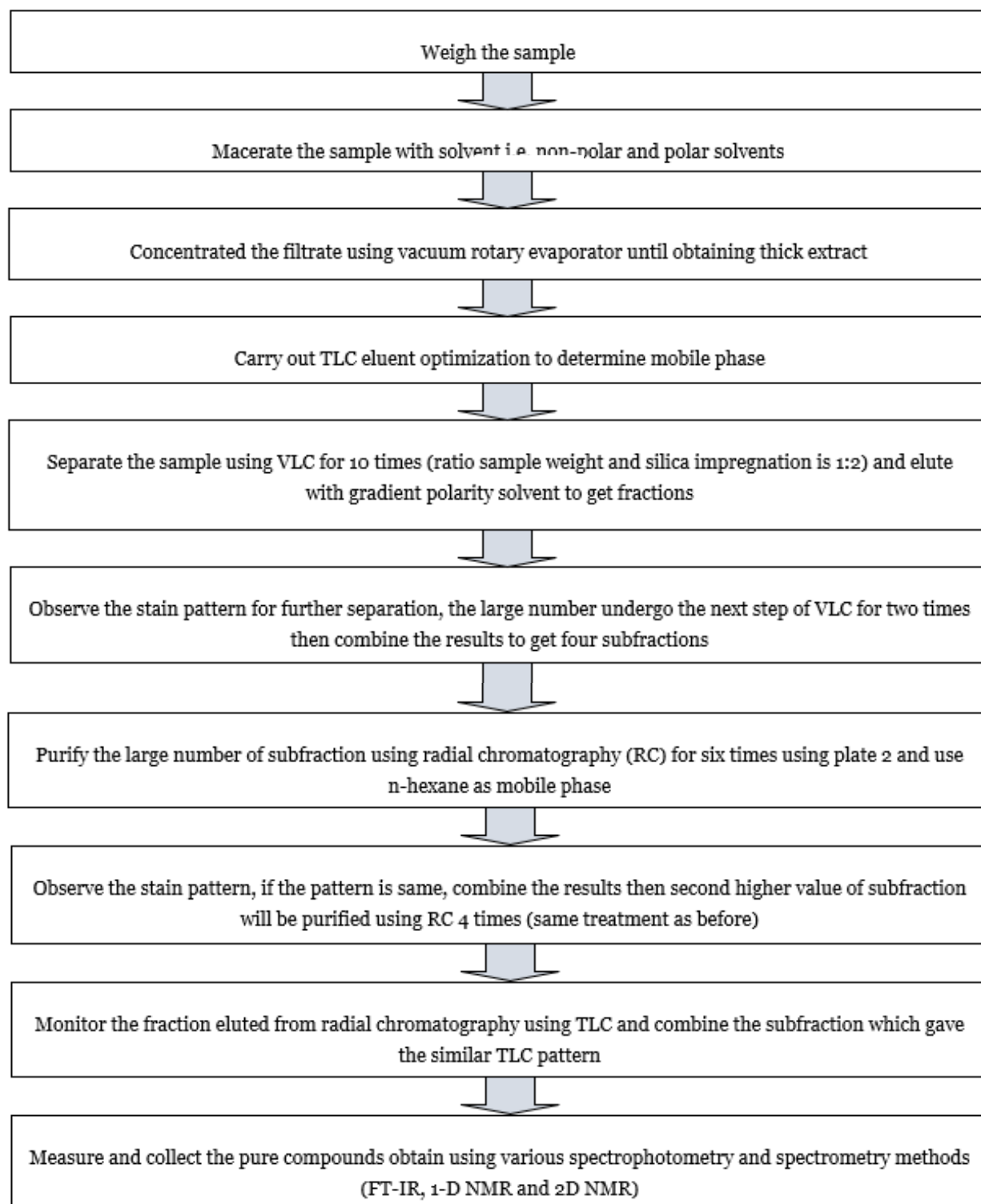
Weigh the sample

Macerate the sample with solvent i.e. non-polar and polar solvents

Concentrated the filtrate using vacuum rotary evaporator until obtaining thick extract

Carry out TLC eluent optimization to determine mobile phase

Separate the sample using VLC for 10 times (ratio sample weight and silica impregnation is 1:2) and elute with gradient polarity solvent to get fractions

Observe the stain pattern for further separation, the large number undergo the next step of VLC for two times then combine the results to get four subfractions

Purify the large number of subfraction using radial chromatography (RC) for six times using plate 2 and use n-hexane as mobile phase

Observe the stain pattern, if the pattern is same, combine the results then second higher value of subfraction will be purified using RC 4 times (same treatment as before)

Monitor the fraction eluted from radial chromatography using TLC and combine the subfraction which gave the similar TLC pattern

Measure and collect the pure compounds obtain using various spectrophotometry and spectrometry methods (FT-IR, 1-D NMR and 2D NMR)

Figure 6: Chromatography techniques to obtain bioactive compounds.

7. Toxicity of Garcinia mangostana

When discussing the issue of toxicity, halal and *toyyiban* products constitute a significant cause of concern, particularly among Muslims. Halal is an Arabic term that implies 'permitted,' 'lawful,' 'approved,' and 'legal.' The *Qur'anic* phrase 'halal' is used to designate the permissible elements. Haram is the polar opposite of halal (forbidden or prohibited).

Between halal and haram, there is a clear distinction (Khattak *et al.*, 2011). *Toyyiban* can be summed up as pure, good and wholesome. Technically, the words 'halal' and '*toyyiban*' have two different connotations. Halal also denotes adherence to the fundamental principles of *Shari'ah*. Yet, the *toyyiban* goes above and beyond these requirements to incorporate improved elements that make something fine, pure, and safe (Abdul Rahman & Sahari, 2022). Nowadays, many products contain

an extract from a questionable source, putting consumers at risk. Even though from halal sources, Muslims are concerned about this issue because if the product is unsafe to use, it will affect consumers in the future. As a result, this laboratory and toxicity test are critical to guarantee that the manufactured product is safe and halal. Plants and the substances derived from them are halal if they are not contaminated with haram nor contain intoxicants (Khattak *et al.*, 2011). The toxicity of an extract used from various sources is a significant concern, especially in cosmetic, medical and food products. Therefore, laboratory and toxicity tests should be conducted to ensure that a product is safe to use, especially for humans.

Determination of the toxicological profile of a substance is an essential prerequisite for guaranteeing public health. Toxicity is the degree to which animals or human beings are affected by a compound, and it may be acute, subchronic or chronic. Acute toxicity causes adverse effects from a single or short-term exposure in an organism. Subchronic toxicity means results that occur for more than a year due to the capability of toxic substances but less than the shelf life of the exposed organism. Chronic toxicity is the power of a substance or a mixture to cause adverse effects, usually after prolonged or continuous exposure, over an extended period (V *et al.*, 2010).

Many rodents and nonrodents, such as rats, pigs, monkeys, rabbits, guinea pigs and dogs, are also used in toxicity studies. Rodents have been the most commonly used species in research due to their low acquisition and maintenance costs (housing and food), standardised hygienic environment, high ethical acceptance, rapid reproductive biology, effective and well-established genetic modification techniques, large-scale standardised phenotyping protocols and access to an extensive database of reference information. Apart from rodents, domestic rabbits (Oryctolagus cuniculus) are the second most frequently used experimental animals because of their low maintenance costs, good reproductive characteristics, and importance as model organisms for translational medicine, even though they have many significant differences from humans like gastrointestinal tract physiology. Other than that, Old World monkeys also used experimental animals such as cynomolgus monkeys *(Macaca fascicularis)* and rhesus monkeys (*Macaca mulatta*) as they are phylogenetically much more similar to primates than humans. Nevertheless, they have significant limitations as animal models due to inadequate ethical recognition, and a long generation interval is among them. Pigs have become standard animal models because they are anatomically, metabolically, physiologically, and pathophysiologically identical to humans, have sound reproduction and are ethically appropriate. A growing number of well-established techniques for genetically modifying pigs, such as lentiviral transgenesis, nuclear transfer from gene-targeted cells, inducible transgene expression, and site-directed nuclease gene editing, now make it easier to create customised broad animal models for diabetes research and other translational medicine applications. While inbreeding may achieve genetic standardisation, as seen in the Massachusetts General Hospital miniature pig, outbred pigs can more closely match human genetic variation. The small size of rodents and rabbits saves money on maintenance and reduces the amount of test compound necessary. Still, it restricts the sample material available per animal, especially in rodents. Minipigs (Göttingen minipig) are a cross between rodents and domestic pigs and are commonly used in drug effectiveness and safety testing. Pigs are the only animals that can approximate the size and weight of humans across a wide variety of developmental stages. Domestic pigs cover infancy and adolescence due to their rapid development as they are

ideal for short and medium terms studies which can take up to several months, while minipig breeds cover adulthood as they are suitable for long-term studies, which can go up to years of the period after they have reached their limit of the growth phase. Medical devices such as bioartificial pancreas, surgical procedures (bariatric surgery) and percutaneous catheter treatments for revascularisation, or noninvasive imaging techniques (ultrasonography, computed tomography, and magnetic resonance imaging) can also be directly used transferred from laboratory studies to clinical use in human patients due to pig size. Unlike pigs, noninvasive imaging techniques in rodents have resolution limitations due to their limited scale, and even ultrasonography necessitates anaesthesia.

Furthermore, noninvasive imaging methods for quantifying islet/beta-cell mass can be evaluated in human-sized pig models, such as decreased beta-cell mass or diet-induced obesity and then checked using quantitative stereological pancreas analyses. Pigs have a large blood volume, which allows for accurate metabolic tests such as glucose/insulin tolerance tests and clamp trials and regular blood sample recovery large enough to conduct complex hormone and metabolite profiling in each sample. Blood samples from pig foetuses or neonatal piglets can be easily obtained. However, assessing stimulated insulin secretion is different in rodents, especially mice, because it is difficult as the sample material limitations restrict the resolution achieved (Renner *et al.*, 2016).

Regarding Shaik & Reddy (2017), in dental treatment, the use of opioid agents helps clean the root canal between appointments and reduce discomfort between appointments. The dentinal tubules are required to penetrate these medications, enter the root canal and inhibit the growth of the bacteria inside the root canal. Irreversible pulpitis is an inflammatory dental pulp disease requiring root canal treatment to clear the microbial infection from the root canal system and the periradicular zone. Treatment of the root canal comprises three steps: preparation of the root canal, which involves cleaning and forming the root canal system; disinfection or sterilization, and obturation of the root canal. Root canal disinfection products appear to induce side effects because they fall into the therapeutic agent group, consist of active chemical agents, and are usually toxic. The herbal-based agent is used as an alternative to lessen the dependence on chemical agents, as almost all countries have also accepted it. The use of traditional medicine in public health care is also advocated by the World Health Organisation (WHO), especially for the prevention and treatment of chronic diseases, degenerative diseases and cases of cancer. It has been proved by previous studies that show the usage of herbal medicine is less toxic as it has comparatively limited side effects than modern medicine/chemical synthesis.

G. mangostana pericarp has been proven by phytochemical research to have the most active ingredients, such as xanthones, flavonoids, saponins and tannins. Pharmacological effects produced by xanthones are antibacterial, antifungal, and anti-inflammatory, and it has been proven non-toxic to mice as it is orally administrated at 100 mg/kg of body weight for seven days. Other research also determined that α-mangostin was non-toxic to human gingival fibroblasts for 480 mins at specific dosages. Tannins are primarily found in several plant species' bark, stems, leaves and fruit and play vital roles in cell defence and growth control. Tannins are also believed to have several elements of chemical activities such as apoptosis, antitumor, antibacterial and antiplasmin. However, tannin can
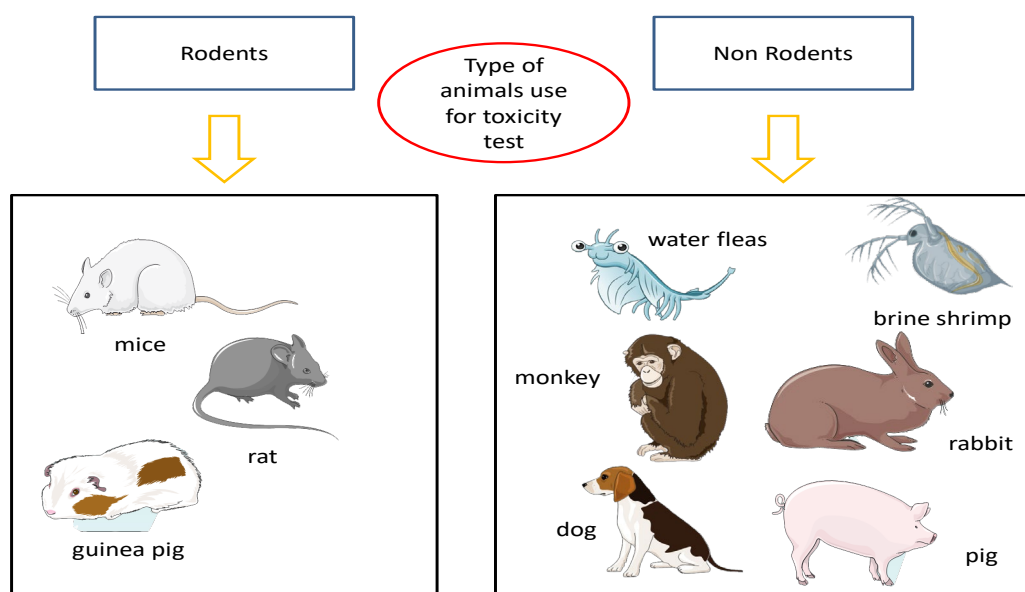
Figure 7: Type of animal used for toxicity test.

cause mucous membrane irritation at high concentrations. These active compounds of *G. mangostana* pericarp extract provide an encouraging potential to promote root canal treatment effectiveness, but all dentistry products must meet biocompatibility criteria. During the initial step of a substance biocompatibility assessment, the toxicity assay is carried out and forms part of the dental material evaluation, and this is one of the procedures needed for standard screening. The toxicity of xanthones and tannins from *G. mangostana* pericarps were determined and contrasted via BHK-21 fibroblast cell culture (Baby Hamster Kidney-21) assay since both xanthone and tannin are the most active ingredients and encourage antimicrobial activities. As a result, it can be concluded that 3.98% of xanthones and 2.2% of tannins were toxic to the culture of BHK-21 fibroblast cells. It is proposed that tannins are more toxic when compared to xanthones.

For nonrodents, daphnia was used to test the toxicity of *G. mangostana* extract. According to Sonawane & George (2018), daphnia is a freshwater filter-feeding crustacean used in ecotoxicity studies because it is a highly susceptible organism. It serves as a model organism for the standard testing protocols of the US Environmental Protection Agency (EPA), the Organization for Economic Cooperation and Development (OECD), and the International Standards Organization (ISO). The *G. mangostana* crude extracts obtained from three different extraction methods (cold extract, Soxhlet extract and microwave-assisted extract) were used to test their toxicity efficacy against *Daphinia magna*. The cytostatic medication 5-fluorouracil has an EC50 value of 15 ppm against *daphnia magna*. Interestingly, some unicellular flagellate organisms grew even at the maximum concentration of extracts (20 ppm). This difference in toxicity begs to be investigated, suggesting that it could be extrapolated to human normal and cancer cell lines.

8. Conclusion

In conclusion, several researchers have described and investigated various bioactivities of *G. mangostana* fruit since long ago. Each of the bioactive components found in *G. mangostana* parts demonstrated a variety of bioactivities that give multiple benefits for human health and wellbeing. The selection of a proper extraction method plays an essential and crucial role in determining the final result and outcome of the study. In addition, each source that will be used on humans must be subjected to a toxicity test to ensure its safety before use.

Acknowledgement

Conflict of interest statement

We declare no conflict of interest.

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