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The Relationship Manilkara zapota, Tumor Necrosis factor Alpha (TNFα) Transforming Growth Factor-β (TGFβ), and Gastric Ulcers

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Abstract

Introduction: Gastric hyperacidity and gastroduodenal ulcers are serious global problems today. A disease found in many people throughout the world and often caused by excessive alcohol consumption. Important factors in the pathogenesis of acute gastric mucosal lesions induced by ethanol. The accumulation of ROS induces oxidative stress and causes gastric inflammation, gastric ulcers and perforation. This will trigger the expression of pro-inflammatory cytokines regulated by NF-κB and Activator protein 1 (AP-1). Interleukin (IL)-1b, IL-6 and tumor necrosis factor alpha (TNFα) are the two main cytokines involved in this inflammatory response.
Objectives: The purpose of writing this review is to determine based on existing literature the effect of administering M. zapota fruit extract on the healing of gastric ulcers of Wistar rats induced by absolute ethanol by determining differences in ulcer scores, ulcer index, and PMN (Polymophonuclear) leukocyte count in the stomach. Wistar rats induced by absolute ethanol and given M. zapota fruit extract, apart from that, also to determine the differences based on the immunoexpression of TNFα and TGF β
Conclusions: Manilkara zapota has attracted attention in relation to the prevention of gastric ulcers. Several studies have shown that Manilkara zapota leaf extract has gastroprotective effects and may protect the gastric mucosa from damage induced by agents such as ethanol. In addition, Manilkara zapota is also believed to have a role in reducing the production of inflammatory factors, such as Tumor Necrosis Factor Alpha (TNFα) and Transforming Growth Factor-β (TGFβ).

Keywords: Manilkara zapota, Tumor Necrosis factor Alpha (TNFα), Transforming Growth Factor-β (TGFβ), Gastric Ulcers

1. Introduction

Gastric hyperacidity and gastroduodenal ulcers are serious global problems today (Zaghlool et al., 2019). A disease found in many people throughout the world and often caused by excessive alcohol consumption, prolonged use of non-steroidal anti-inflammatory drugs (Ren et al., 2021).
Gastric ulcers occur if damage to the mucosal layer up to the muscularis mucosa is found in a round or oval shape with a diameter of 0.3 cm – 0.6 cm, due to the disruption of the integrity of the gastric mucosa (Kumar et al., 2018b ; Pangarapean & Akil, 2014).
Ethanol not only directly damages gastric mucosal cells but also stimulates the gastric mucosa to produce excessive stomach acid. In addition, mast cells in gastric tissue will release large amounts of histamine which in turn will stimulate histamine receptors in parietal cells to produce excessive acid. Alcohol also induces inflammation while reducing antioxidant activity and protective mucus (Yeo et al., 2021).
Research conducted by Ren et al., 2021, shows that an imbalance of aggressive and defensive factors is the basis for gastric damage as shown in figure 1. Inflammatory mediators and Reactive Oxygen Species (ROS), are important factors in the pathogenesis of acute gastric mucosal lesions induced by ethanol. The accumulation of ROS induces oxidative

stress and causes gastric inflammation, gastric ulcers and perforation. This will trigger the expression of pro-inflammatory cytokines regulated by NF-κB and Activator protein 1 (AP-1). Interleukin (IL)-1b, IL-6 and tumor necrosis factor alpha (TNFα) are the two main cytokines involved in this inflammatory response. The formation of ROS during the inflammatory process, whereas ROS not only directly damages cell structure but also increases the production of pro-inflammatory factors. During the development of gastric ulcers, pro-inflammatory cytokines and the influence of ROS synergize, underlying the occurrence of lesions. Therefore, anti-oxidants and anti-inflammatories play an important role in protecting the gastric mucosa against injury (Leyva-López et al., 2016; Raish et al., 2021; Ren et al., 2021).
The prevalence of gastric ulcers is influenced by socio-economics, demographics, gender and age (Rijal et al., 2016). Worldwide, it is estimated that there are around 4 million cases of gastric ulcers (Selmi et al., 2017). The incidence in several countries is; United States around 4.5 million (20%) every year (Nuraida et al., 2020). The highest is Spain 141.8/100,000 people, the lowest is England 23.9/100,000 people, every year (H. Azhari, 2018). Incidence data for several regions in Indonesia for large cities; Medan (North Sumatra) 91.6%, Jakarta 50%, Denpasar 46%, Palembang 35.5%, Bandung 32.5%, Aceh 31.7%, Surabaya 31.2% and Pontianak 31.2% (Nuraida et al., 2020).
2018 World Health Organization (WHO) data, Indonesia is in fourth place in the world after Cambodia, Central Africa, and Sierra Leone. and second in Asia after Cambodia, based on a peptic ulcer death rate of around 4.95 per 100,000 population (WHO, 2018). Ulcers that occur in the stomach, the healing process begins in 2-3 days. The initial stages of migration of epithelial cells are important and re-epithelialization of the mucosal surface, and reconstruction of the gastric glands. Granulation tissue begins to develop at the base of the ulcer within 48-72 hours (2-3 days) after ulceration. Tumor Growth Factor Beta (TGFβ) plays an important role in fibroblast migration, proliferation, increased synthesis of collagen and fibronectin. The complete epithelial replacement process takes around 3-7 days, while complete replacement of gland cells takes months (Fornai et al., 2011; Tarnawski, 2005; Tarnawski & Ahluwalia, 2021). About 1% of gastric ulcers can become cancerous (Y. Liu et al., 2017). Gastric Ulcer Treatment aims to reduce pain, treat ulcers, prevent recurrence of ulcers, and prevent complications (Paguigan et al., 2014).

2. Objectives

The purpose of writing this review is to determine based on existing literature the effect of administering M. zapota fruit extract on the healing of gastric ulcers of Wistar rats induced by absolute ethanol by determining differences in ulcer scores, ulcer index, and PMN (Polymophonuclear) leukocyte count in the stomach. Wistar rats induced by absolute ethanol and given M. zapota fruit extract, apart from that, also to determine the differences based on the immunoexpression of TNFα and TGF β in the stomachs of Wistar rats induced by absolute ethanol and given M. zapota fruit extract and also differences based on the expression of TNFα and mRNA. TGFβ in the stomach of Wistar rats induced by absolute ethanol and given M. zapota fruit extract.

3. Sapodilla (M. zapota) as a Potential Plant

M. zapota in Indonesia is known as sapodilla; in India, Malaysia, Singapore it is known as ciku (Chikoo); Bahamas is called Dilly; Puerto Rico is called Niespero; English called Sapodilla; Elsavador is called Muyozapot; the West Indies country is known as Naseberry; Brazil is known for sapoti/sapotilha; Cuba is known as Sapota/sapote; Thailand is known for Lamoot; Mexican Chicopote/Chicozapote; Siriname is known as Mispu (Karle Pravin & Dhawale Shashikant, 2019). This tree can bear fruit all year round, is large and shady and can grow up to 30-40 meters. Cultivation is carried out on the island of Java by grafting or by seed (Devatkal et al., 2018).
M. zapota can be planted in the lowlands up to an altitude of 1200 meters above sea level. Sapodilla plants are optimally cultivated in areas with wet to dry climates. The best type of soil for sapodilla plants is sandy loam (latosol) which is fertile, loose, has lots of organic material, good aeration and drainage. The degree of soil acidity (soil pH) that is suitable for the development of sapodilla plants is between 6-7. The depth of groundwater that is suitable for the development of sapodilla plants is between 50 cm and 200 cm. (Eny D Kusmiyati et al., 2014).
The M. zapota Sawo plant is a medium to large sized tree with a large branching system (sympodial type). Initial growth is slow but after a few years it can reach a height of up to 20-30 meters. All parts of the tree can secrete sap known as chicle which is milky white in color. Root system: M. zapota roots are shallow with most of the roots found in the surrounding soil. Leaves: The leaves are evergreen and arranged in a spiral (measuring 7-12x2-4cm), light brown when young and turning light-dark green when old. Flowers: small, bisexual, bell-shaped (10 mm diameter), grow singly or in groups in leaf axils near branches. Fruit: brown, almost round and varies in width from 5-10 cm. The unripe fruit is hard and rough while it becomes soft and juicy when ripe. Seeds: Some sapodilla fruits are seedless but usually produce 3-12 seeds per fruit. The seeds are hard and brown or black with one white edge. Reproductive System: includes out-breeding species (crossing between unrelated individuals) and self-incompatibility (incompatibility between male and female reproduction). The flowers are bisexual and the stigma grows outside the corolla so cross-pollination can occur easily. Flowers occur due to cross pollination by other sapodilla varieties and produce fruit throughout the year. It takes about 4

months for the fruit to ripen. Seedlings begin to bear fruit after 5-8 years, while grafted varieties flower earlier (2-3 years from planting). Sapodilla is pollinated by insects. The sapodilla pollinator is Hermitia spp. Honey bees also visit sapodilla flowers which in turn are involved in pollination (Mehnaz & Bilal, 2017). Hard, immature sapodilla can last for 9 - 10 days, rotting in 2 weeks, but very low temperatures can inhibit ripening and damage the fruit. Low relative humidity causes the fruit to wrinkle and shrivel. Sapodilla can be stored for a long time under the right conditions. Harvested fruit can be stored for 2 to 3 weeks at 12 -16 °C. Storage with 5% CO2 for 18 days at normal temperature. Ripe fruit can be stored for six weeks (Mehnaz & Bilal, 2017). The sweet fruit can be obtained all year round, people know it because it has an ellipsoidal shape and is shaped roughly like an apple, so it is often called sapodilla apple. The weight is very different from large, good fruit, the skin weighs 25 grams, and the fruit weighs 150 grams and the seeds weigh about 1 gram. One manila sapodilla fruit contains 30% tannin, 30% triterpenoids, 30% flavonoids, and 10% water (Salnus, 2019).

4. M. zapota as Traditional Medicine

Indonesia, as a country with natural resources that is second in biodiversity in the world after Brazil, has the opportunity to become a producer of products that rely on natural raw materials. Indonesia has around 30,000 plant species that have been identified and 950 of them are known to have the potential to be developed as medicines, food supplements, cosmetics and nutritional pharmaceuticals (nutraceuticals) (Mufti et al., 2017). Traditional medicine has been recognized as useful in supporting modern medicine systems. Entering this era of globalization, technological developments and forms of use of medicinal plants in Indonesia are growing very rapidly with a demand volume of 1000 medicinal plants per year. Indonesia's position as the second largest "Mega Biodiversity" in the world after Brazil, has very diverse tropical plants and marine biota (Mufti et al., 2017).
In Indonesia there are around 30,000 types of plants and 7,000 of them are thought to have medicinal properties. The World Conservation Monitoring Center has reported that Indonesia is an area where many types of medicinal plants are found, while the number of plants that have been used has only reached 2,518 types. Indonesia has a variety of cultures and regional traditions. There is an ancestral legacy that has been passed down from generation to generation which still provides traditional treatment for various diseases (Mukhriani et al., 2018). This treatment utilizes various medicinal plants found in the environment around where you live. The existence of a view regarding "Back to Nature", namely the use of traditional medicines from various medicinal plants found in the surrounding environment, means that a lot of scientific research and scientific information needs to be provided to prove the potential of various types of medicinal plants in Indonesia to improve health and the economy. in Indonesia (Mukhriani et al., 2018).

Traditionally the use of M. zapota is world renowned for its nutritional value and medicinal properties. The fruit as well as various parts of the tree have been used traditionally to treat various diseases (Tulloch et al., 2020). The health benefits of manilkara zapota fruit are not limited to the edible parts but the contents that provide active biological principles in it. The leaves are used to treat coughs, colds and diarrhea. The leaves are used to treat coughs, colds, diarrhea while the decoction is used for fever, bleeding, wound healing and gastric ulcers (Ma et al., 2003). The bark of the tree contains gummy white chicle, which was used for the production of chewing gum and in dental surgery in the 18th century (Yee & Shukkoor, 2019). The fruit is used to treat lung diseases and the bark to treat dysentery and diarrhea. (Karle et al., 2021). It has biological activities such as anti-inflammatory, anti-cancer, anti-bacterial, anti-rheumatic and anti-bacterial (BC et al., 2019). The tannin content of raw fruit helps overcome stomach disorders. (Karle Pravin & Dhawale Shashikant, 2019). The seeds are a febrifuge, febrifuge, tonic and have been used in the elimination of bladder and kidney stones. The bark is known for its astringent and febrifuge properties and a decoction has been used for diarrhea, dysentery and fever (Riaz et al., 2020a).

Several areas in Indonesia that have used manila sapodilla as a treatment for typhoid fever using the method of pressing grated raw fruit and then drinking the juice for typhoid sufferers are several areas on the island of Java such as Jogjakarta, Solo, Batu Malang. Several areas on the island of Kalimantan such as Samarinda and Balikpapan and several areas in South Sulawesi such as Sinjai, Bulukumba, Bone and Sidrap (Mufti et al., 2017). A plant with potential as a medicine is manila sapodilla (M. zapota). The chemical compounds contained in manila sapodilla fruit are tannins, flavonoids and triterpenoids. Sapodilla seeds contain saponin, and the fruit contains a lot of potassium, energy, carbohydrates, vitamins (A, C, B6), magnesium and phosphorus. Boiled young fruit can be used to stop diarrhea, the leaves are used to treat fever, medicine for coughs, colds, wounds and ulcers, and the flowers are used as a spice for women who have just given birth. Infusions of young fruit and flowers are drunk to relieve lung complaints, while tea made from the bark can be used as a medicine to reduce fever and stop diarrhea and dysentery. Crushed seeds have diuretic power and can relieve bladder infections and kidney stones (Fayek, Monem, et al., 2012).
A liquid extract from crushed sapodilla seeds is used in Yucatan as a sedative and sleeping pill. A decoction of sapodilla leaves is mixed with sweet chayote and drunk every day to lower blood pressure. The efficacy of M. zapota as a medicine is due to the tannin, flavonoid and teriterpenoid content in the stems, leaves and even fruit, so it can be said to be good as

an alternative natural diarrhea medicine. Besides that, the leaves contain saponin and the stems contain tannin. The sap of the sapodilla fruit can also be used to mix candy. Extracts from young fruit have many benefits and have social potential in health services as traditional or antimicrobial medicines. The sap of the fruit, young fruit and leaves can be used as a medicine for diarrhea. The leaves and stems of sapodilla contain flavonoids (Kamaraj et al., 2019).
Manila sapodilla (M. zapota) originates from tropical areas of Central America and Mexico. In Indonesia, this plant is often found in yards. This plant is a gummy tree. Based on research results, sapodilla fruit is one of the plants used as a medicine for diarrhea (Eny Dwi Kusmiyati et al., 2014). Several communities in South Kalimantan, especially North Hulu Sungai Regency, use sapodilla fruit as a traditional medicine to treat diarrhea (Vishwasrao et al., 2017). The sapodilla fruit used by the community is young fruit. The sapodilla fruit is grated and then the water is taken to drink. Based on the literature, sapodilla fruit (Manilkara zapota.) contains tannins which can protect the intestinal mucosal walls against stimulation of intestinal contents or precipitate toxins, this can help with overall anti-bacterial power (Pientaweeratch et al., 2016).

5. Chemical content contained in M. zapota

Based on phytochemical tests (Idrus et al., 2020), it shows that young M. zapota fruit contains flavonoid, tannin and triterpenoid compounds. Examination of manila sapodilla fruit simplicia resulted in a water content of 15.33%, total ash content of 1.89%, acid insoluble ash content of 0.95%, ethanol soluble juice content of 37.45%, water soluble juice content of 38 .01%. The results of the phytochemical screening of one 120 gram sapodilla fruit showed the presence of 30% flavonoids, 35% triterpenoids and 35% tannins. The content of tannins, flavonoids and triterpenoids in sapodilla fruit which can function as an antibacterial, the results of the TLC (Thin Layer Chromatography) test show that 100 grams of sapodilla fruit extract contains 30% tannin compounds, 35% flavonoids and 35% saponins. Meanwhile, the ethanol extract of sapodilla bark contains alkaloids, flavonoids, saponins and tannins. The similarities in the results obtained can be caused by the similarity in the use of the solvent, namely ethanol, and the extraction method used, namely the maceration method (Mondal et al., 2012).
The nutritional content of sapodilla fruit per 100 grams can be seen in the table below:

Table 1. Chemical components in M. zapota per 100 grams (Izwady et al., 2018; Julian F, 2019; Salnus, 2019)

COMPONENT	RATE
Water content	69,0 – 75,7%
Ascorbic acid	8,9-41.4 mg/ 100 gr
Total acid	0.09 – 0,15%
pH	5.0- 5.3
Total dissolved solids	17.4-23.7 B rix
Glucose	5.84- 9.23 %
Fructose	4.47 – 7.13 %
Sucrose	1.48 – 8.75 %
Total Sugar	11.14- 20.43%
Starch (kanji)	2.98 -6.40 %
Tannin	3.16-6.45%

6. Chemical content contained in M. zapota

Tumor necrosis factor alpha (TNFα) is a cytokine that has pleiotropic effects on various cell types. After identification, TNFα is the main regulator of the inflammatory response and is known to be involved in the pathogenesis of several inflammatory and autoimmune diseases. Structurally, TNFα is a homotrimeric protein consisting of 157 amino acids, mainly produced by activated macrophages, T lymphocytes, and natural killer cells (Jang et al., 2021). TNF is first produced as a 26 kDa 233-amino acid transmembrane protein (mTNF) that is expressed on the cell surface, where it persists or is actively broken down by the TNF converting enzyme producing a 17 kDa 157-amino acid soluble form (sTNF) which is then released and can be detected in blood plasma. Tumor necrosis factor (TNF) forms mTNF and sTNF are mediated by one of two receptors, namely TNFR1 and TNFR2. TNF receptor 1 (TNFR1) is expressed in all human tissues. TNF receptor 2 (TNFR2) is expressed primarily in immune cells, neurons, and endothelial cells. Transmembrane TNF (mTNF) functions as a ligand that transmits cell-to-cell interactions and when bound to TNFR2 as its main biological target is able to induce a stronger response than sTNF. Interestingly, mTNF also functions as a receptor by initiating cell signaling cascades through outside-in signaling. The structures of TNFR1 and TNFR2 have extracellular similarities in the mTNF- and sTNF-binding areas, but have different intracellular characteristics. The tail of TNFR1 in the cytoplasm

contains a Death Domain (DD), so that TNFR1-associated DD (TRADD) is related to TNFR1. In contrast, TNFR2 does not have intracellular DD but has TNFR-associated factors (TRAF) 1 and 2 instead. TNFR1 and 2 signaling can lead to the activation of nuclear factor kappa-B (NF-κB) and the induction of a cell survival response. TNFR1 is also capable of inducing a cell death response depending on the physiological response. However, regulation of both TNFRs depends on the cellular environment and is not fully understood (Holbrook et al., 2019; Rolski & Błyszczuk, 2020; Zhang et al., 2019).

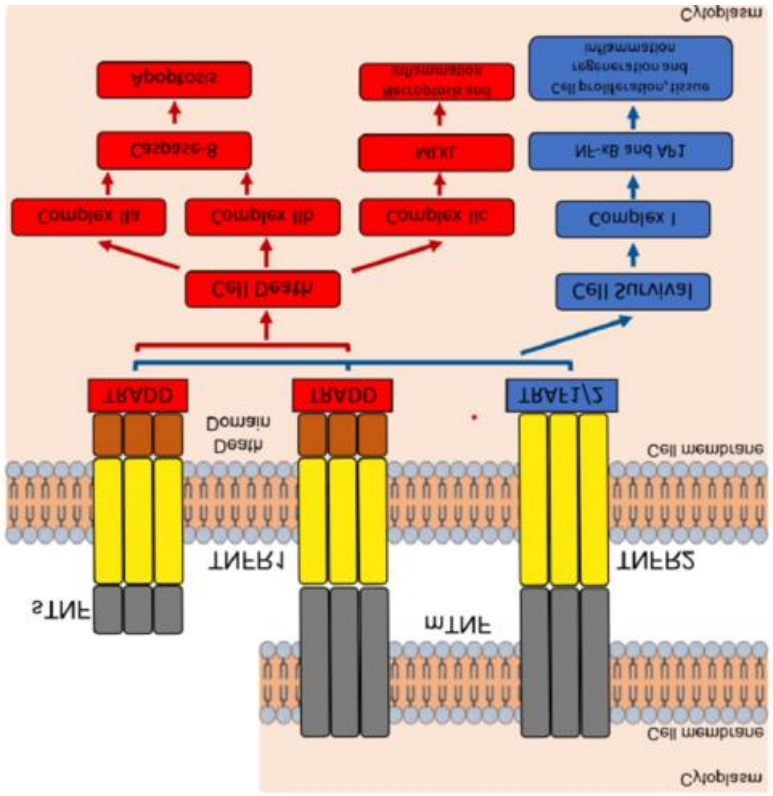

Figure 1. Tumor necrosis factor-α (TNFα) signaling pathway mediated by the two main receptors of TNFα, namely TNFR1 and TNFR2 (Holbrook et al., 2019; Jang et al., 2021)

When TNFR1 is active, which interacts between the receptor and the enzyme serine/threonine-protein kinase 1 (RIPK1), cells experience apoptosis (via complex IIa and IIb), necrosis (via complex IIc), cell survival (via complex I). The formation of complexes IIa and IIb causes cleavage of pro-caspase-8 to form caspase-8 which induces apoptosis. When the IIc complex is formed, activating the kinase domain-like protein (MLKL) will induce necroptosis. After formation of complex I, cell survival is induced through activation of nuclear factor kappa-B (NF-κB). However, active TNFR2 will interact directly with TNFR-associated factors (TRAF) 1 and 2 to induce complex I formation by inducing homeostatic signals (Holbrook et al., 2019). TNFα is a pleiotropic cytokine that plays a role in the inflammatory process, initiating polymorphonuclear (PMN) and activating it so that PMN can reach the site of infection. Tumor necrosis factor alpha (TNFα) is the main cytokine in the acute inflammatory response to Gram-negative bacteria and other microbes (Ozkan et al., 2018)

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7. Review of Transforming Growth Factor-β (TGFβ) in Wound Healing

Transforming growth factor-β (TGFβ) is a 25-kDa disulfide-linked homodimeric peptide. Three isoforms (TGFβ1 - β2 and - β3) have been identified that share 64–85% amino acid sequence homology. TGFβ1 is the common form and is found almost everywhere. Other isoforms are expressed in a more restricted range of cells and tissues. The genes encoding TGF β1, - β2 and - β3 are located at 19q13, 1q41 and 14q24, respectively. While TGFβ stimulates fibroblast proliferation, it can inhibit cell proliferation in various cells (e.g. epithelial cells and endothelial cells). Also involved in suppressive and inflammatory immune responses. TGFβ alters immunity in a variety of conditions. (Lu et al., 2014; TANIGAWA et al., 2005)

TGFβ controls the proliferation, survival, activation, and differentiation of B cells, as well as the development and function of innate cells, including natural killer (NK) cells, macrophages, dendritic cells, and granulocytes. Collectively,

TGF-β plays an important role in maintaining peripheral tolerance to self and harmless antigens, such as food, commensal bacteria, and fetal alloantigens, and in controlling the immune response to pathogens (Xu et al., 2018).

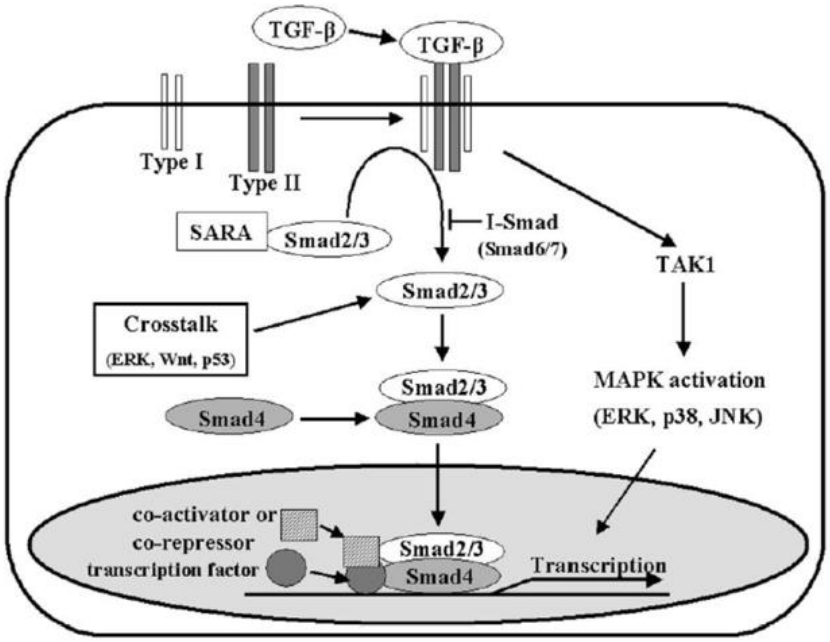

Figure 2. TGF β signaling pathways (T. Tanigawa et al., 2005; Tzavlaki & Moustakas, 2020).

The central mechanism of the signal transduction system by the TGF (Tumor Growth Factor) receptor follows the process of receptor-mediated interaction and phosphorylation. Therefore, TGF is first associated with homodimeric TGF RII, which acts as a receptor, the interaction of which causes conformational adaptation between the ligand and TGF RII, a high-strength binding area, then formed for TGF RI on the side of the ligand and TGF RII. After recruitment of two TGF RI units, the type II receptor kinase phosphorylates a serine in the TGF RI juxtamembrane subdomain marked with glycine and serine (GS) in turn activating the type I receptor kinase. The type II receptor phosphorylates the GS domain of the type I receptor. The type I receptor is then activated specifically phosphorylates Smad2/3. Phosphorylated Smad2/3 forms a complex with Smad4. This Smad complex translocates into the nucleus and participates in transcriptional regulation. The presence of cross-talk between other pathways modulates the TGFβ-Smad signaling pathway, which includes the MAPK, Wnt and p53 pathways. The Smad signaling pathway is essential for most TGFβ responses by cross-talking with the Smad signaling pathway. TGFβ has been shown to activate extracellular signal-regulated kinase (ERK)-1, ERK-2, p38 or c-Jun amino-terminal kinase (JNK) also known as mitogen-activated protein kinases (MAPKs) (15-17). The Smad-independent TGFβ pathway is partially mediated by TAK1, a MAPK kinase kinase (T. Tanigawa et al., 2005; Tzavlaki & Moustakas, 2020)
In humans TGFβ regulates host response systems and inflammation. For example, leukocytes as myeloid cell derivatives use germline-encoded receptors to detect molecular patterns associated with pathogens, which allows them to alert and activate the rest of the immune system, including adaptive immunity. Alternatively, lymphocytes of the adaptive immune system express antigen-specific receptors that distinguish small differences in macromolecules and build long-term immunity by forming immunological memory (Liarte et al., 2020).

8. The relationship between Manilkara zapota, Tumor Necrosis factor Alpha (TNFα) Transforming Growth Factor-β (TGFβ), and Gastric Ulcers.

Gastric ulcer injury will manifest as inflammation in the stomach due to injury or injury, disruption of the regulation of the body's defense system, then inducing the body's defense system in the form of an inflammatory response. TNFα and TGFβ are two important cytokines involved in immune regulation and inflammatory responses. TNFα and TGFβ also have bidirectional functions in the regulation of host defense and participation in inflammation. These functions can vary depending on the cellular environment (Yoshimatsu, Wakabayashi, et al., 2020).
Consuming alcohol causes oxidative stress, which results in increased reactive oxygen species (ROS), stress on the endoplasmic reticulum (ER), which is associated with gastric mucosal lesions including gastritis, gastric ulcers and malignancy. Although the mechanisms by which gastric ulcers occur are not fully understood, evidence suggests that proinflammatory cytokines, oxidative stress, and apoptosis play an important role. Along with increasing

myeloperoxidase (MPO) activity, neutrophil activation is associated with an increase in the inflammatory response in the form of expression of nuclear factor kappa B (NF-κB), which also controls the formation of the cytokine TNFα which contributes to gastric mucosal damage. This event strengthens the inflammatory cascade by triggering the release of pro-inflammatory mediators, increasing the recruitment of macrophages and neutrophils, thereby exacerbating gastric tissue damage. Increased lipid peroxidation and reduced glutathione (GSH). glutathione peroxidase (GPx) and total antioxidant capacity (TAC). At the same time, there is increased apoptosis and loss of mucosal epithelial cells as well as reduced cytoprotection of the gastric mucosa, namely; prostaglandin E2 (PGE2) and nitric oxide (NO) also worsen stomach damage (Chen et al., 2016; Hany H et al., 2015).

The synergistic effect of TNFα and TGFβ is largely manifested in jointly promoting the release of inflammatory factors. In astrocytes, co-stimulation of TNFα and TGFβ increased NOS-2 expression compared with cytokine stimulation alone. TNFα and TGFβ can synergistically increase IL-6 secretion in IEC-6 cells. In mesenchymal stem cells TNFα and TGFβ can increase the release of proinflammatory factors such as COX-2, that is, in the presence of TNFα, TGFβ is converted into proinflammatory cytokines, and when they act together on MSCs, they can play a synergistic effect in promoting inflammation. In addition, TGFβ can reverse the inhibitory effect of MSCs on T cell proliferation, and cooperate with TNFα to enhance the immune response (Z. W. Liu et al., 2022)

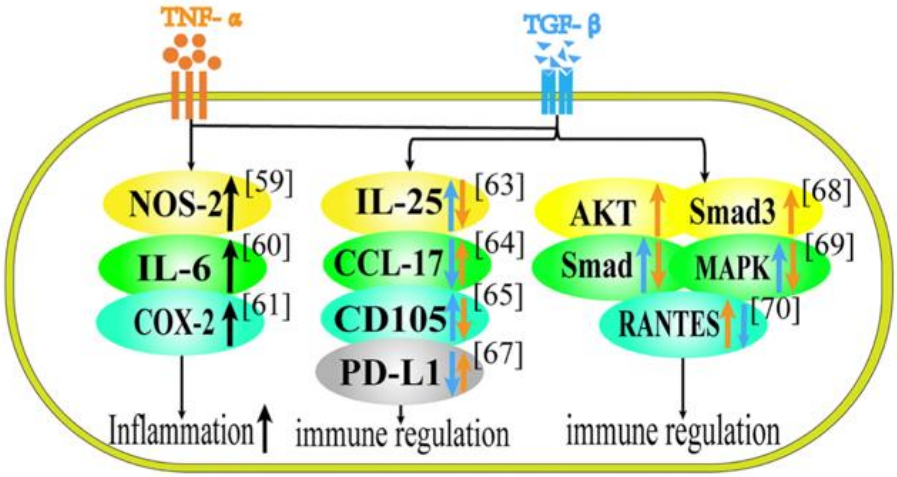

Figure 3. Role of TNF-α and TGF-β in Inflammation and Immune Regulation (Z. W. Liu et al., 2022).

Regulatory effects of TNFα and TGF-β on different proteins in terms of immune regulation. Black arrows represent the general regulatory effects of TNFα and TGFβ. The orange arrow represents the effect of TNFα, and the blue arrow represents the effect of TGFβ (Figure 3). Antagonistic effects of TNFα and TGFβ have been reported in terms of immune regulation and inflammatory responses. Regarding the antagonism of the two cytokines, studies have shown that in inflammatory bowel disease (IBD), TNFα can inhibit the synthesis of IL-25, whereas TGFβ can stimulate the upregulation of IL-25 in colon tissue. TGFβ can inhibit the production of CCL-17 in human epidermal cells induced by TNFα, indicating that TGF-β may have a certain effect on the treatment of gastric inflammation (Yoshimatsu, Kimuro, et al., 2020).

TNFα can downregulate CD105 expression, whereas TGFβ can upregulate it in vascular endothelial cells and this differential expression can regulate repair of endothelial cell damage. TGFβ secreted by human umbilical cord mesenchymal stem cells can inhibit TNFα and relieve atopic dermatitis. In patients with systemic lupus erythematosus (SLE), exogenous TNFα can restore PD-L1 expression on lupus cells, while TGFβ, on the other hand, can inhibit PD-L1 expression on lupus cells (Yoshimatsu, Kimuro, et al., 2020). Talking about the antagonism of the two cytokines in their respective pathways, increased TNFα can lead to activation of AKT, and activated AKT can interact with Smad3, leading to the inhibition of the TGFβ pathway in regulatory T cells, so that TNFα can attenuate the differentiation and function of Treg cells induced by TGFβ in autoimmune diseases via AKT and Smad3 signaling pathways. In fibroblasts, TNFα can inhibit TGFβ-induced activation of Smad2/3 and p38 MAPK pathways and stop the expression of nerve growth factor (NGF), which inhibits the regeneration of fibroblast cells. neurons. In rheumatoid synovial fibroblasts, TGFβ inhibits TNFα-induced RANTES expression in a dose-dependent manner, likely due to decreased binding of NF-κB to the RANTES promoter (Yoshimatsu, Wakabayashi, et al., 2020).

The complexity of TNFα and TGFβ can increase the release of inflammatory factors and play pro-inflammatory or anti-inflammatory effects on different cells and tissues. In epidermal cells and patients with systemic lupus erythematosus,

TNFα is proinflammatory and TGFβ is anti-inflammatory. In vascular endothelial cells, inflammatory bowel disease, T cells and fibroblasts, TNFα is anti-inflammatory and TGFβ is pro-inflammatory (Yoshimatsu, Wakabayashi, et al., 2020). The mechanism of action between TGFβ and TNFα in healing gastric ulcers is complex and diverse. TGFβ, a master regulator of tissue repair, is essential for gastric ulcer healing, as evidenced by its high expression in patients with healed ulcers (S. Shih et al., 1999; Shih, 2005; T. Tanigawa et al., 2005). It exerts its effects by binding to its receptors, especially the TGFβ II receptor, and activating various signaling pathways (S. Shih et al., 1999; T. Tanigawa et al., 2005). The expression of TGFβ and its receptors increases during ulcer healing, indicating their importance in this process (Milani & Calabrò, 2001)(Stadnicki et al., 2009). However, the specific interaction between TGFβ and TNFα in gastric ulcer healing still requires further investigation.

Several studies have shown an association between the severity of gastric ulcers and increases in proinflammatory cytokines (IL-1β, IL-6, and TNFα). The flavonoid content of M. zapota has a role in evaluating inflammatory processes, such as the expression of adhesion molecules, ICAM-1 and P-selectin, and inducible endothelial cell surface molecules involved in leukocyte adhesion, namely flavonoids can reduce inflammatory processes associated with ulcerative, so it can reduce the severity of the disease (Akanda et al., 2018; Farzaei et al., 2015; Serafim et al., 2020).

The interaction of TNFα, TGFβ, tannins, and flavonoids in gastric ulcers involves mechanisms that influence each other in a complex manner. Tannin, as a natural product, forms a protective layer in the stomach, increases resistance to injury and has antioxidant and anti-inflammatory properties (de Jesus et al., 2012; Demarque et al., 2018). TGFβ, a growth factor, improves ulcer healing by promoting cell migration, angiogenesis, and extracellular matrix production (Gönül et al., 2004; T. Tanigawa et al., 2005). Flavonoids, another group of natural compounds, have been shown to have antiulcer and gastroprotective effects, possibly through their anti-inflammatory and antioxidant properties (Martín et al., 2000; Vasconcelos et al., 2010). The role of TNFα in gastric ulcer formation is associated with NF-kappaB activation and subsequent tissue damage (T. Takeuchi et al., 2002).

9. Conclusion

Manilkara zapota has attracted attention in relation to the prevention of gastric ulcers. Several studies have shown that Manilkara zapota leaf extract has gastroprotective effects and may protect the gastric mucosa from damage induced by agents such as ethanol. In addition, Manilkara zapota is also believed to have a role in reducing the production of inflammatory factors, such as Tumor Necrosis Factor Alpha (TNFα) and Transforming Growth Factor-β (TGFβ). In the context of gastric ulcers, polymorphisms in TNFα are associated with an increased risk of gastric ulcers and gastric cancer in Japanese. In contrast, IL-1beta did not show a significant relationship. Therefore, TNFα has become the main focus in research regarding the risk and development of gastric ulcers. Meanwhile, consideration of the role of TGFβ in gastric ulcer healing is also important, taking into account the cellular and molecular mechanisms involved in the healing process.

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11. Conflict of Interest

There is no conflict of interest in this study.

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