

Therapeutic Potential of Mastic and Pomegranate Peel in Helicobacter pylori Eradication and Gastrointestinal Repair: A Comparative Review

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I. Abstract

Helicobacter pylori is a Gram-negative bacterium with a spiral shape that has evolved to colonise the gastric mucus layer due to its various virulence factors, including urease and CagA/VacA cytotoxic proteins. This results in consistent chronic inflammatory processes within the stomach, as well as, progressive damage to stomach tissue due to these processes. Persistent infections are characterised by greater secretion levels of pro-inflammatory cytokines, such as IL-1 β and TNF- α , and the establishment of oxidative stress due to the accumulation of reactive oxygen species (through reactive oxidative stress, ROS), causing an imbalance between damage and repair processes within the digestion tract. Although effective strategies for eradicating the bacteria have emerged based on the use of triple/quadruple antibiotic regimens, increasing rates of bacterial resistance, which is highest to clarithromycin/metronidazole, have limited the sustained success of complete eradication of infection. As a result, there continues to be increased interest in identifying natural agents that contain high levels of bioactive secondary metabolites to provide dual therapeutic strategies for targeting the bacteria and supporting the healing of tissue. Mastic gum has a wide variety of mono- and diterpenes, such as α -pinene, β -myrcene and Linalool, as well as triterpenoid acids like Masticadienonic acid and Isomasticadienonic acid which have been shown to inhibit H. pylori growth through disruption of the cell membrane and inhibition of urease activity. Similarly, these compounds have been proven to reduce expression of virulence factor genes and reduce inflammation by inhibiting the NF- κ B pathway. On the other hand, Pomegranate Peel (Punica granatum) is also rich in polyphenolic compounds with high concentrations of ellagitannins (Punicalagin and Punicalin) as well as ellagic acid and gallic acid, which both exhibit antioxidant and antimicrobial properties. Furthermore, these compounds inhibit bacterial growth through protein precipitation, bacterial enzyme disruption, neutralization of free radicals, and reduction in oxidative stress. Lastly, Pomegranate Peel promotes mucosal repair via stimulation of epithelial cell proliferation and enhancement of the amount of mucosal protective mucus produced. Both Mastic Gum and Pomegranate Peel exhibit antibacterial, immunomodulatory, and antioxidant effects through complex biological mechanisms. The chemical structures of the terpenes in Mastic Gum and the polyphenols in Pomegranate Peel are significantly different. Thus, the bioactive patterns of Mastic Gum and Pomegranate Peel vary considerably. Mastic Gum has more of a direct bactericidal effect, while Pomegranate Peel is bacteriostatic but has a more pronounced cellular protective effect. Bioavailability and intestinal absorption of the active compounds may also vary with respect to their in vivo effectiveness. Furthermore, the dosage and type of extract (alcoholic vs. aqueous) of the active compound will determine the therapeutic efficacy. Thus, the ability of these compounds to help restore microbial balance by interaction with the



gut microbiota is also an important factor. Their impact on cellular signaling pathways associated with inflammation and oxidative stress further indicates that these compounds may play a role in the repair of the digestive system. We must emphasize how critical it is to create multi-target therapies aimed at destroying pathogens while also allowing the body to heal damaged tissues through various mechanisms such as regeneration (regrowing) muscle, collagen, connective tissue, etc.) as a result of pathogen destruction. These medicines should help us to decrease our dependence on traditional antibiotics and lessen any resistance to them. Additionally, these findings create a strong case for utilizing plants to create a combined approach to modern medicine and herbal medicine. To ensure that we utilize these combinations effectively in clinical practice, we must first identify any pharmacological differences between mastic gum and pomegranate peel before we can identify possible therapeutic applications of either agent. In this regard, understanding how each substance acts is critical for developing effective multi-target therapy systems in the future..

II. Introduction

Helicobacter pylori, an adaptive microorganism, germinates in the extreme acidity of the stomach. Its biochemistry includes an elaborated enzyme system that allows for extended survival and colonization within the mucus. One key enzymatic system of this microorganism is urease. Urease catalyzes the hydrolysis of urea to ammonia and CO₂, thus locally changing the pH in the neighborhood of the bacteria so as to promote their survival [1]. These same microorganisms also secrete a variety of proteins that disrupt epithelial cell integrity by causing the disruption of tight junctions as well as activating numerous complex inflammatory pathways, such as the activation of NF-κB as well as the production and secretion of inflammatory cytokines such as IL-8 [2]. This sustained exposure leads to the development of a state of constant inflammation with the subsequent increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) which further exacerbate the oxidative damage to proteins, lipids, and nucleic acids [3]. Imbalance between pro-oxidative factors and anti-oxidant systems (such as glutathione and superoxide dismutase (SOD)) is an important factor that contributes to developing ulcers and precancerous lesions in the stomach lining. In spite of conventional treatment protocols using proton pump inhibitors (PPIs) with antibiotics (clarithromycin and amoxicillin), the increasing genetic mutation rate of bacteria (i.e., 23S rRNA) has caused a significant reduction in response rates. In addition, side effects associated with this type of treatment disrupt the gut microbiome and encourage researchers to investigate potential multi-targeted therapy options based on natural products. Mastic gum is a unique example of a combination of resin-based materials consisting of many terpenes (α -pinene, β -pinene, and terpinen-4-ol) and triterpenes (oleanolic acid and masticadienonic acid), which have antibacterial properties by altering cell membrane permeability and inhibiting essential enzymes. Studies indicate that these compounds can inhibit urease activity in the bacterium, therefore preventing it from adapting to the acidic environment of the body. Mastic gum also has anti-inflammatory properties by reducing the expression of inflammatory mediators and inhibiting cellular signaling pathways associated with oxidative stress. In contrast, pomegranate peel is a great source of effective phenolic compounds (punicalagin, ellagic acid and gallic acid) classified as ellagitannins that have a high capacity for neutralizing free radicals. These compounds also exhibit antibacterial activity by interacting with bacterial membrane proteins resulting in their precipitation and disrupting their vital functions [5]. Additionally, these compounds help to inhibit the formation of biofilms, which is a major contributor to bacterial resistance to treatment. Furthermore, pomegranate peel has been shown to promote tissue repair through stimulating epithelial cell proliferation and increasing the expression of growth factors such as VEGF. It also helps to lessen oxidative stress by increasing the activity of some antioxidant enzymes and reducing the buildup of reactive oxygen species. The different chemical makeup of the two substances,



mastic gum (which is high in terpenes) versus pomegranate peel (which is high in polyphenols), is reflected in the manner in which they interact with human biology. Terpenes usually affect the cell membrane of bacteria directly while polyphenols exert multiple effects, including inhibition of enzymes, modulation of signals within cells, and are also considered to be protective against oxidation (6). One more difference between these two types of compounds has to do with how they are absorbed by our bodies; because of the various structures present, many polyphenols undergo extensive metabolic processes in the intestine prior to being absorbed into the bloodstream. These two types of chemical substances also have an impact on the gut microbiome; they will promote the growth of beneficial bacteria while inhibiting the growth of pathological bacteria. Therefore, this effect is considered important for restoring the functional balance of the digestive tract. Research also indicates that the effective use of combining antifungal, anti-inflammatory, and immunostimulatory effects may help control chronic infections. However, the need for a better understanding of how these naturally sourced compounds work is growing, as well as how to best utilize them in an evidence-based therapy. Determining the proper dosage and extracting the right amount are two areas needed for additional research. Also, the potential interactions between these natural products and conventional medications warrant an appropriate evaluation to assure they are safe and effective. The use of natural products is growing in popularity as a means of reducing the use of antibiotics and is therefore consistent with the principles of integrative medicine. Thus, the need to study the biological activity of plants that possess multiple types of activity, particularly those that have both direct benefits to healing and those that promote the healing processes in the body, is increasingly apparent. Pomegranate peel and mastic gum are two well-studied examples of this class of compounds because both have antibacterial, anti-inflammatory and antioxidant activities, therefore providing an opportunity to create novel treatment options against *H. pylori* and its related diseases. [7].

1.1. Objective of the Study

The objective of this research is to investigate the biological properties of pomegranate peel and mastic gum against *Helicobacter pylori*, primarily by determining how various active ingredients found in the two plant sources (terpenes— α -pinene; masticadienonic acid, and ellagitannins—punicalagin; ellagic acid) affect their molecular mechanisms. The study will provide insight into how these different types of ingredients (terpenes and polyphenols) interact with the *H. pylori* bacteria to inhibit their virulence factors (urease and CagA). Additionally, this research will examine how these ingredients can help reduce oxidative stress and regulate both ROS and NF- κ B inflammatory signal pathways. This investigation will also assess how these ingredients may assist in repairing the gastric mucosa and promoting cell regeneration. Ultimately, the purpose of this work is to develop a scientific basis for using pomegranate peel and mastic gum as an integrative alternative to decrease the dependence on traditional antibiotics..

2. Medicinal Plants

1.2.1 Scientific Nomenclature of the Plants

Pistacia lentiscus var. *chia* (Mastic Gum) belongs to the *anacardiaceae* family, and is harvested as a resinous substance from the trunks of trees extensively grown throughout the Mediterranean Basin [8]. *Punica Granatum* (Pomegranate) belongs to the *Lythraceae* family, and the fruit peel contains the highest level of bioactive compounds of pharmaceutical value [9]. Both plants have been used for centuries in various traditional medicines, and recent studies have concentrated on the molecular characteristics of these plants, as well as identifying the active compounds responsible for the biological property of these two plants. [10].

1.2.2 General Description

When dry, mastic gum is a clear, solid, resinous material that can be used for medicinal purposes. The presence of mastic gum's antimicrobial and anti-inflammatory properties can be attributed to the many different types of aromatic compounds it is composed of. Mastic gum is produced by the tree through secretion from glandular ducts as a response to environmental stress. Pomegranate peels, although they are actually a tertiary portion of the fruit (functionally), have an extremely high number of phenolic compounds relative to the fruit's pulp or seed, allowing them to have the ability to produce biological effects across broad ranges (i.e., they exhibit broad-spectrum pharmacological activity). Pomegranate peels are also noted for their capacity to resist being oxidized because they contain large quantities of hydrolyzable tannins. [12].

1.2.3 Definition of Bioactive Compounds

Mastic gum contains several classes of active components: mono-, di-, and triterpenes, including α -pinene, β -myrcene, masticadienonic acid have shown that they interact with bacterial cell membranes and disrupt critical functions. Other active components in mastic gum are known to inhibit the activity of important enzymes, including urease; thus limiting the ability of *H. pylori* to survive [13]. Pomegranate peel contains several important active compounds, including ellagitannins (e.g., punicalagin and punicalin) and ellagic acid. These components have been shown to precipitate proteins, inhibit microbial enzymes, modulate inflammatory pathways, and reduce oxidant stress at the cellular level. [14].

1.2.4 Chemical and Nutritional Composition

Mastic gum has a composition containing a majority (85%) of volatile oils (Monoterpenes), triterpenes, and phenolic compounds that are the main contributors to its antibacterial and immunomodulatory properties [15]. Mastic gum also contains fatty acids and organic acids that enhance its stability in the stomach. Pomegranate peel has a composition of high levels of polyphenols (mainly hydrolyzable tannins), flavonoids, organic acids, and mineral components (specifically potassium and calcium) that provide pomegranate peel with significant nutritional and functional properties, especially with regard to antioxidant activities and supporting epithelial tissue structure. [16].

1.3 Antioxidants

Cells are shielded from damage through either preventing or repairing oxidative stress by antioxidants, which neutralize ROS while minimizing their effect on cellular structures (e.g. lipids, proteins and nucleic acids). Important in this respect are phenolic compounds (e.g. ellagitannin [punicalagin] and flavonoids) found within the pomegranate peel, as they have a high capacity for electron donation and stabilizing free radicals. Similarly, the action of terpene compounds (e.g. α -pinene and masticadienonic acid) present in mastic gum support antioxidant system enhancement by decreasing levels of free radicals and regulating cellular defense enzymes. The presence of antioxidants afterwards will promote the integrity of the gastric mucosa and assist in decreasing tissue damage caused by chronic inflammatory conditions associated with *H. pylori* infection. Oxidants/antioxidants provide a means to improve cellular repair processes by offering an alternative approach to achieving balance between oxidants and their equivalents. Therefore, antioxidants serve as a primary component in the mechanism of action for both naturally sourced and therapeutic benefits. [17].

1.3.1 Antidiabetic Effect

Mastic gum and pomegranate peels both exhibit antihyperglycemic activity via several mechanisms, including the improvement of insulin sensitivity and regulation of glucose absorption from the intestine. Punicalagin, a phenolic compound present in pomegranate peels, has been shown to inhibit the alpha-glucosidase enzyme responsible for breaking down carbohydrates, thus slowing down carbohydrate digestion and preventing an increase in post-prandial (after eating) blood glucose levels. α -Pinene (a terpenoid) and other terpenes modulate cellular signalling pathways involved in glucose metabolism. Both mastic gum and pomegranate peel seem to improve pancreatic beta cell function and reduce oxidative stress associated with metabolic disorders; therefore, they can help regulate blood sugar levels and support normal metabolic function. [17].

1.3.2 Laxative or Astringent Effect on the Intestine

Pomegranate peel exhibits an astringent effect on the intestine due to its high content of hydrolyzable tannins such as ellagitannins, which reduce intestinal fluid secretion and decrease intestinal motility. In contrast, some components of mastic gum may show a modulating effect on intestinal motility by improving the microbial environment and reducing intestinal inflammation. This balance helps improve digestive system function without causing acute disturbances in motility. The astringent effect of pomegranate peel can be beneficial in cases of infection-associated diarrhea, while the laxative effect is indirectly based on improving mucosal health, reflecting the difference in effect depending on the chemical composition of each substance [18].

1.3.3 Hepatoprotective Effect

The active compounds in mastic gum and pomegranate peel contribute to liver protection by reducing oxidative stress resulting from ROS accumulation. Polyphenols like ellagic acid enhance the activity of antioxidant enzymes such as glutathione peroxidase, while terpenes reduce hepatic inflammation by inhibiting inflammatory mediators. These compounds help maintain the integrity of liver cells against toxin-induced damage. They also show the ability to inhibit lipid peroxidation in liver cell membranes, thereby enhancing vital liver functions and maintaining its physiological balance [19].

1.3.4 Preventive Effect on the Liver

The preventive effect on the liver is among the most prominent biological properties associated with both mastic gum and pomegranate peel. Active compounds work to reduce the accumulation of free radicals within liver cells, limiting the initiation of chronic inflammatory processes. Terpenes found in mastic gum, such as masticadienonic acid, contribute to inhibiting signaling pathways associated with inflammation like NF- κ B, leading to reduced production of inflammatory cytokines. In contrast, polyphenols in pomegranate peel play a pivotal role in liver protection through their ability to neutralize reactive oxygen species (ROS) and improve the efficiency of cellular defense systems. Compounds like punicalagin and ellagic acid work to reduce lipid peroxidation, a key biomarker of liver cell damage. These compounds contribute to supporting mitochondrial integrity and maintaining intracellular energy production. They also help enhance the expression of cell-protective proteins such as heat shock proteins. An important aspect of this preventive effect is its ability to reduce the leakage of liver enzymes into the blood, such as ALT and AST, reflecting the preservation of cell membrane integrity. These compounds also show an effect in regulating the immune response within the liver by modulating the activity of resident immune cells like Kupffer cells. This leads to a reduction in the excessive inflammatory response that could lead to liver fibrosis. Furthermore, these compounds contribute to improving the balance between oxidants and antioxidants within the liver tissue. They also work to inhibit the formation of toxic compounds resulting from the metabolism of chemicals. Evidence suggests that the continuous use of plant compounds rich in polyphenols and terpenes may contribute to the long-term prevention of chronic liver diseases. These compounds may also support liver cell regeneration processes by stimulating growth factors. They also show the ability to improve hepatic blood flow and enhance metabolic functions. Together, these effects represent an integrated mechanism for protecting the liver from damage caused by environmental and pharmaceutical factors [20].

1.3.5 Protection Against Nephrotoxicity

Active compounds in both mastic gum and pomegranate peel contribute to reducing nephrotoxicity by reducing oxidative stress within the kidney tissue. Polyphenols like punicalagin inhibit ROS production, thereby protecting tubular cells from damage. These compounds also enhance the activity of antioxidant enzymes such as catalase and superoxide dismutase. In turn, terpenes contribute to improving kidney function by reducing local inflammation. They also help maintain the integrity of cell membranes in the kidney and reduce the accumulation of toxic substances resulting from drug metabolism. They show the ability to reduce proteinuria, an indicator of glomerular damage. They also work to improve the glomerular filtration rate (GFR). They contribute to inhibiting inflammatory pathways associated with NF- κ B activation within the kidney tissue. They also protect mitochondria from toxin-induced damage. They help reduce chronic oxidative stress associated with exposure to toxic substances. They enhance the kidney's ability to regenerate and self-repair. Thus, these compounds exhibit a multi-level protective effect against nephrotoxicity, supporting their use as adjunctive agents for maintaining urinary system health [21].

1.4 Chemical and Physical Properties

Both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) are characterized by complex chemical and physical properties that are directly reflected in their biological behavior and therapeutic efficacy. Chemically, mastic gum contains a rich mixture of terpene compounds such as α -pinene, β -myrcene, and terpinen-4-ol, in addition to triterpenes like masticadienonic acid and oleanolic acid, which give it lipophilic properties and solubility in organic solvents more than in water [22]. Pomegranate peel, on the other hand, consists mainly of various polyphenols, most notably punicalagin, punicalin, ellagic acid, and gallic acid, which are hydrophilic compounds with a high capacity to form hydrogen bonds with biological molecules [23]. Mastic gum is characterized as a hard resin that turns into a viscous substance when heated and partially dissolves in ethanol and organic solvents, reflecting its relatively non-polar nature [24]. In contrast, pomegranate peel is distinguished by a fibrous composition rich in cellulose and hemicellulose, with a high tannin content that gives it astringent properties and physical effects on mucous membranes [25]. Density and moisture also differ between the two substances, as mastic gum has lower moisture and greater thermal stability compared to pomegranate peel, which contains a higher percentage of heat-labile compounds [26]. These physical properties affect the extraction methods and bioavailability of the active compounds. Organic solvents are preferred for extracting mastic gum components, while aqueous or hydroalcoholic solvents are used to extract pomegranate peel compounds [27]. Furthermore, the molecular size and charge distribution of the active compounds affect their ability to penetrate biologically and interact with cell membranes [28].

1.4.1 Chemical and Physical Properties Subsections

The chemical properties of mastic gum include high proportions of mono- and diterpenes characterized by a non-polar cyclic structure, contributing to their ability to merge with bacterial lipid membranes [29]. They also contain triterpenoid acids responsible for anti-inflammatory and antimicrobial biological activity [30]. Pomegranate peel is characterized by an abundance of multiple phenolic bonds in its compounds, which give it a high chelation capacity with metals and enzyme inhibition [31]. Tannins contribute to the formation of protein complexes that reduce membrane permeability and inhibit the growth of microorganisms [32]. Regarding physical properties, mastic gum is characterized by its hardness at low temperatures and flexibility when heated, in addition to its friability into a fine powder that is easy to use in pharmaceutical preparations [33]. Pomegranate peel is characterized by its high drying capacity and long-term preservation without significant loss of active compounds, due to its low moisture content after drying [34]. The dark color of pomegranate peel reflects its richness in oxidized phenolic compounds, while the relative transparency of mastic gum reflects the non-polar nature of its terpene compounds [35]. These combined properties affect the stability of the compounds during storage and processing, as well as their biological efficiency upon use [36].

1.5 Effects of Plant Extracts

Extracts of both mastic gum and pomegranate peel exhibit broad-spectrum biological activity depending on the chemical composition and the type of solvent used in the extraction [37]. Extracts rich in terpenes from mastic gum show a high ability to inhibit *H. pylori* growth by disrupting cell membrane integrity [38]. They also inhibit urease activity and reduce the bacterium's ability to adapt to the acidic environment [39]. Pomegranate peel extracts, rich in polyphenols, show potent antioxidant activity, in addition to inhibitory effects on bacterial growth by disrupting vital proteins and enzymes [40]. These extracts contribute to reducing inflammation by inhibiting NF- κ B pathways and lowering levels of inflammatory cytokines [41]. They also enhance the regeneration of epithelial cells and improve mucosal integrity [42]. Efficacy greatly depends on the concentration of active compounds and the preparation method, as alcoholic extracts typically lead to better extraction of active compounds compared to



aqueous extracts in some cases [43]. The synergy between different compounds within the extract also plays an important role in enhancing biological activity [44]. Studies indicate that concentrated extracts may have a stronger effect than single compounds due to the synergistic effect [45]. Thus, these extracts represent a promising option for multi-target therapeutic applications [46–47].

1.6 Mechanism of Action

The mechanism of action of both mastic gum and pomegranate peel relies on a complex interplay between direct effects on the bacterium and indirect effects on the biological environment of the digestive system [48]. Terpene compounds in mastic gum penetrate the bacterial cell membrane due to their hydrophobic nature, leading to increased membrane permeability and leakage of vital cellular components [49]. These compounds also inhibit urease activity, reducing the ability of *H. pylori* to modify the acidic medium [50]. In contrast, polyphenol compounds in pomegranate peel interact with bacterial proteins via hydrogen bonds and hydrophobic interactions, leading to the disruption of vital enzyme functions [51]. They also contribute to inhibiting the formation of biofilms, one of the most important mechanisms of bacterial resistance [52]. At the cellular level, these compounds affect signaling pathways such as NF- κ B and MAPK, leading to a reduced inflammatory response [53]. They also play a role in reducing the production of reactive oxygen species (ROS) and improving the intracellular antioxidant balance [54]. Together, these mechanisms enhance the protection of the gastric mucosa and stimulate tissue repair processes [55]. Immunological effects also include modulating the activity of immune cells such as macrophages and lymphocytes [56]. Evidence suggests that the interplay between antibacterial, anti-inflammatory, and antioxidant effects forms the basis of the biological efficacy of these compounds [57]. Thus, the mechanism of action is embodied in a multi-target model that combines eliminating the pathogen and supporting the healing environment within the digestive system [58].

1.7 Effects of the Two Plants on Metabolism

Both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) exhibit notable effects on metabolic processes through the interaction of their active compounds with energy regulation pathways and nutrient metabolism within the body. Terpenes found in mastic gum, such as α -pinene and masticadienonic acid, contribute to improving insulin sensitivity by affecting cellular signaling pathways associated with insulin receptors and activating AMPK, thereby enhancing glucose uptake in peripheral tissues. These compounds also reduce oxidative stress, a key factor in metabolic disorders, by lowering ROS levels and improving mitochondrial efficiency in ATP production. In contrast, polyphenols in pomegranate peel, such as punicalagin and ellagic acid, play a role in inhibiting carbohydrate-digesting enzymes like α -amylase and α -glucosidase, leading to slowed glucose absorption in the intestine and regulated postprandial glycemic response. They also contribute to improving the lipid profile by lowering total cholesterol and triglyceride levels through effects on lipid biosynthesis pathways in the liver [59]. These compounds also modulate gene expression related to metabolism, including genes regulating fat storage and energy expenditure. Furthermore, they affect the gut microbiome, which positively reflects on overall metabolic balance. Evidence suggests that the combined effect of these compounds leads to improved balance between catabolism and anabolism. It also contributes to reducing chronic low-grade inflammation associated with metabolic disorders [60]. This reflects an integrative role between antioxidant and immunomodulatory properties in supporting metabolic functions. Mastic gum shows an effect more closely related to regulating cellular signals, while pomegranate peel is distinguished by its direct effect on metabolic enzymes and nutrient absorption. The bioavailability of the compounds also plays a role in determining their extent of effect within the body. Thus, these natural compounds represent adjunctive agents in improving metabolic efficiency and preventing disorders associated with poor metabolism. Their importance is particularly evident in conditions related to insulin resistance and metabolic syndrome [61].



2.4 Effect of the Plant Extracts on Liver Tissues of Male Rats

Liver tissues are among the most affected tissues by bioactive compounds due to their pivotal role in metabolism and detoxification. Extracts of both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) have shown clear effects on the functional and histological structure of the liver in male rats. The active compounds in mastic gum, such as monoterpenes (α -pinene and β -pinene) and triterpenes (masticadienonic acid and oleanolic acid), work to reduce oxidative stress within hepatocytes by enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, thereby limiting the accumulation of reactive oxygen species (ROS). These compounds also contribute to inhibiting lipid peroxidation within cell membranes, which preserves the integrity of the membrane structure of hepatocytes and prevents cell necrosis. In contrast, pomegranate peel extracts contain effective polyphenolic compounds such as punicalagin, ellagic acid, and gallic acid, characterized by their high ability to neutralize free radicals and chelate transition metals that stimulate oxidative reactions. These compounds work to reduce elevated liver enzyme levels such as ALT, AST, and ALP, which are biomarkers of hepatocyte damage during stress or toxicity. Studies have also shown that these extracts contribute to improving the histological organization of the liver by reducing inflammatory infiltration in the liver tissue and reorganizing the arrangement of hepatocytes around the central veins. The active compounds also affect molecular pathways associated with inflammation, inhibiting the NF- κ B pathway and reducing the production of inflammatory cytokines such as TNF- α and IL-6, thereby alleviating the chronic inflammatory response. Furthermore, these compounds contribute to maintaining mitochondrial integrity by reducing the oxidative stress associated with the electron transport chain, thus improving intracellular energy production. Improvements in indicators of liver fibrosis have also been observed as a result of reduced collagen deposition and inhibition of hepatic stellate cell activation. Mastic gum extracts show a supportive effect in enhancing bile flow and regulating metabolic processes associated with the liver, contributing to improved overall liver function. Meanwhile, pomegranate peel supports detoxification processes by stimulating Phase II detoxification enzymes. These compounds also contribute to reducing nitrosative stress alongside oxidative stress, thereby enhancing comprehensive protection of liver tissue. Histological results indicate a clear reduction in degenerative changes such as cellular swelling and necrosis when using these extracts. Improved regularity of hepatic cords and preservation of the normal structure of liver lobules have also been observed. These effects demonstrate that both extracts possess the ability to support cellular regeneration in the liver by stimulating growth factors and reducing factors that inhibit cell division. The synergy between antioxidant and anti-inflammatory properties is believed to play a key role in these protective effects. The difference in the nature of the active compounds between terpenes and polyphenols leads to a diversity of biological mechanisms that work in an integrative manner. These results reflect the importance of dosage and extraction method in determining the intensity of the histological effect. They also indicate the potential use of these extracts as supportive agents for liver protection in cases of exposure to toxins or oxidative stress. These effects are particularly prominent in male rat models used to study physiological responses related to hormonal metabolism. Thus, these natural compounds represent a promising option in reducing liver damage and enhancing the histological and functional integrity of the liver [62–66].



2.4.1 Variation in the Effect of Extracts According to Plant Origin and Harvest Time, and Divergence of Researchers' Opinions

The effect of plant extracts from both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) shows marked variation depending on the plant's origin, growth conditions, and harvest time. Environmental factors such as temperature, humidity, soil type, and exposure to biotic stresses affect the chemical composition of the active compounds. Additionally, the season during which plant materials are collected leads to changes in the concentrations of secondary metabolites such as terpenes in mastic gum and polyphenols in pomegranate peel, which is reflected in the biological activity of the extracts. Some studies have shown that plants grown in moderately stressful environments produce higher concentrations of defensive compounds such as α -pinene and punicalagin, due to the activation of secondary metabolic pathways. In contrast, optimal growth conditions may relatively reduce these compounds due to a decreased physiological need for their production. Harvesting, drying, and storage methods also play a pivotal role in maintaining the stability or causing the decomposition of active compounds. Researchers' opinions have varied regarding the best time for extracting active substances. Some believe that harvesting at advanced maturity stages gives the highest concentration of phenolic compounds, while others indicate that early harvesting may preserve more biologically active compounds. Results have also differed between studies due to variations in extraction methods used, whether aqueous, alcoholic, or using organic solvents, which affect the quality and quantity of extracted compounds. The geographical diversity of plant sources leads to genetic and chemotype variations reflected in the chemical composition. Some research indicates clear variation in biological efficacy even among samples of the same plant species, while other studies confirm that general effects remain similar despite partial compositional differences. This variation is attributed to the complex interaction between environmental, genetic, and technical factors. Therefore, interpreting study results requires considering all these factors together when comparing different extracts. This variation is considered one of the main reasons for differing research recommendations regarding the optimal use of these plant materials [67–70].

2.4.2 Effect of Extract Treatment on Body Weight and Weight Change in Male Rats

Body weight and rate of weight change are important biological indicators for assessing general physiological status and response to various treatments in animal models. Extracts of both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) have shown varying effects on these indicators in male rats. These effects are directly related to the ability of active compounds, such as terpenes in mastic gum and polyphenols in pomegranate peel, to modulate metabolic processes and regulate energy balance within the body [71]. In many studies, it has been observed that administration of pomegranate peel extracts rich in punicalagin and ellagic acid may contribute to reducing weight gain resulting from high-fat diets, by inhibiting fat and carbohydrate digesting enzymes and reducing nutrient absorption [72]. These compounds also contribute to improving insulin sensitivity and regulating glucose levels, which positively reflects on weight stability [73]. In contrast, some studies have shown that mastic gum extracts may have a moderate effect on weight, maintaining physiological balance without significant changes, attributed to their anti-inflammatory effect and improvement of digestive system functions [74]. Terpenes such as α -pinene and oleanolic acid may also contribute to improving metabolic efficiency by activating AMPK pathways and increasing fatty acid oxidation [75]. On the other hand, a group of researchers indicated that some plant extracts may not cause significant changes in weight, especially when used at low doses or for short periods, as metabolic effects are believed to need a longer duration to appear clearly [76]. This view also suggests that the effect of extracts may greatly depend on the initial physiological state of the animals, such as age, metabolic activity level, and diet [77]. In contrast, another group of researchers confirmed that pomegranate peel extracts



specifically may contribute to weight loss or limit weight gain by affecting the gut microbiome, promoting the growth of beneficial bacteria associated with improved metabolism [78]. They also indicated that phenolic compounds may reduce low-grade inflammation associated with obesity, which is reflected in reduced fat accumulation [71]. Some results show that the effect on weight may also be related to the ability of these compounds to reduce appetite or modulate hunger and satiety signals. However, other studies have not recorded significant differences in weight between treated and untreated groups, indicating variation in results. This variation may be attributed to differences in extraction methods, concentration of active compounds, and the type of animal strain used in experiments. The duration of the experiment also plays a crucial role in determining the appearance of effects on weight, as changes may be gradual and require long-term follow-up. Some results suggest that effects on weight may be indirect, resulting from improved metabolic functions rather than a direct effect on fat storage. Thus, it can be said that the effect on body weight and rate of change reflects a complex interaction between the biochemical and functional factors of the plant extracts. The divergence of researchers' opinions reflects the diversity of experimental models and laboratory conditions used. Understanding these effects still requires further comparative studies that comprehensively consider influencing factors. These results are important in evaluating the safety and efficacy of plant extracts when used for long periods. They also contribute to determining appropriate doses to achieve a balance between efficacy and the absence of negative effects on the general condition of the organism.

2.4.3 Effect of Extract Treatment on Relative Weights of Liver and Kidneys in Male Rats

The relative weight of both the liver and kidneys is an important indicator for evaluating the physiological and toxic effects of plant compounds, as any change in these weights reflects alterations in tissue size or functional status resulting from exposure to the extracts. Extracts of both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) have shown varying effects on the relative weights of these organs in male rats, related to the properties of the active compounds such as terpenes and polyphenols [79]. Regarding the liver, some studies indicate that the use of pomegranate peel extracts rich in punicalagin and ellagic acid may contribute to reducing the relative weight of the liver in cases of oxidative stress, as a result of reducing inflammation and fat accumulation within hepatocytes [80]. These compounds also improve metabolic functions and reduce degenerative changes, which reflects on the stability of the relative liver weight. In contrast, mastic gum extracts have shown a supportive effect in maintaining the relative liver weight within normal limits, attributed to their ability to reduce oxidative stress and inhibit inflammatory pathways. Regarding the kidneys, some results have shown that pomegranate peel extracts may contribute to maintaining normal relative kidney weight by reducing the accumulation of toxic compounds and improving the oxidative balance within the kidney tissue [81]. Phenolic compounds may also protect tubular cells from damage, limiting abnormal enlargement or shrinkage of the kidney. In contrast, some studies indicated that mastic gum extracts do not cause significant changes in the relative weight of the kidneys, indicating a high degree of safety and a non-harmful effect on kidney tissue [82]. Some researchers believe that any change in relative weights may be related to the dose of the extract and duration of exposure, in addition to the initial health status of the animals. Another group of studies confirms that the observed effects on relative weights mostly reflect functional improvement rather than harmful structural changes [83]. This may be attributed to the role of these compounds in reducing inflammation and improving blood circulation within vital organs. They also contribute to regulating metabolic processes and reducing oxidative stress, thereby maintaining tissue balance. Thus, the effect of plant extracts on the relative weights of the liver and kidneys can be considered an indicator of their protective efficacy, not necessarily a toxic effect, especially when used within the studied doses [83].



2.4.4.1 Histological Effects of the Two Plant Extracts on Liver Tissues

Histological studies demonstrate great importance in evaluating the biological effects of extracts of both mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) on the fine structure of the liver, as they provide direct indicators at the cellular and tissue levels regarding the extent of protection or damage. The results of histological examinations in male rats have shown that treatment with these extracts leads to a clear improvement in the architectural organization of the hepatic lobules compared to untreated groups [84]. These extracts contain active compounds such as terpenes in mastic gum and polyphenols in pomegranate peel, which play a pivotal role in reducing oxidative stress and protecting hepatocytes from damage. A decrease in manifestations of cellular degeneration such as cellular swelling and vacuolar degeneration has been observed, indicating a clear protective effect on cellular structure. These compounds also contributed to reducing inflammatory infiltration within the liver tissue, which is an indicator of a decreased inflammatory response. Some histological sections showed improvement in the regularity of hepatic cords and the return of cells to their normal arrangement around the central veins. In contrast, some studies have shown that pomegranate peel extracts rich in punicalagin and ellagic acid may be more effective in reducing histological changes associated with oxidative stress compared to some other extracts [85]. These compounds also inhibit inflammatory pathways such as NF- κ B, which is reflected in reduced infiltration of inflammatory cells into the liver tissue. Mastic gum extracts have shown a role in enhancing cell membrane stability and reducing lipid peroxidation, thereby preserving the integrity of hepatocytes. A group of researchers indicated that these effects may vary depending on the dose and duration of treatment, as the protective efficacy increases with increased exposure time within certain limits [86]. Another group believes that some differences in histological results may be due to variations in preparation methods and concentrations used in the plant extracts. Some results also show improvement in histological markers associated with cellular regeneration, suggesting the potential of these extracts to support liver tissue repair processes. These changes reflect a decrease in damage indicators and an increase in preserving the normal structure of the lobules. Thus, it can be concluded that the plant extracts possess a clear protective effect on liver tissues, manifested in reducing inflammation and oxidative stress and improving overall histological organization [87].

III. Conclusions

The integrated results indicate that combining extracts of mastic gum (*Pistacia lentiscus*) and pomegranate peel (*Punica granatum*) shows an integrative effect in supporting general health and reducing disorders associated with oxidative stress and inflammation. It has been shown that active compounds such as terpenes in mastic gum and polyphenols in pomegranate peel act through multiple pathways, including enhancing the cellular antioxidant system and reducing free radical production. This combination also contributes to improving metabolism by regulating glucose and lipid levels, thereby supporting metabolic balance and reducing its disturbances. Data showed improvement in biomarkers associated with liver function, with a decrease in enzymes indicative of damage and improvement in histological structure. This was also reflected in the relative weights of vital organs within normal limits, indicating no obvious toxic effects at the studied dosage. These extracts contributed to reducing abnormal histological changes while preserving the structural organization of liver and kidney cells. It is noted that the anti-inflammatory effects played a pivotal role in reducing cellular infiltration and improving tissue response. The combination also demonstrated the ability to modulate body weight indicators in a manner consistent with improved general metabolic status. The results reflect an integrative interaction between the chemical components of both plants, enhancing biological efficacy compared to using each extract individually. The effect on the gut microbiome may also contribute to supporting these results by improving absorption and regulating vital processes. Data indicate that the response may vary depending on the dose, duration of use, and physiological state of the organism. However, the general effects remain positive within the framework of cellular protection and reduction of oxidative damage. Overall, the combination of mastic gum and pomegranate peel can be considered a promising option to support metabolic and protective functions in the body. This combination also represents a model of integration between multi-mechanism plant compounds to achieve potential therapeutic effects. These results support the trend towards studying composite plant formulations as an effective strategy in biological and preventive applications.



IV. References

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