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Review

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Preventive and Therapeutic Effects of *Punica granatum* (Pomegranate) in Respiratory and Digestive Diseases: A Review

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Abstract: The pomegranate fruit is made of white to deep purple seeds that are enclosed in a white, spongy, astringent membrane, also known as pericarp, covered by a thick red skin and a crown-shaped calyx. It contains a variety of beneficial ingredients, including flavonoids, ellagitannin, punicalagin, ellagic acid, vitamins, and minerals. Pomegranates possess numerous health benefits, and their use in disease treatment has been widely recognized since antiquity. This fruit was known to exhibit several biological properties, including antibacterial, anti-inflammatory, antioxidant, and anticancer activities. Pomegranate has been used in a variety of medical systems for the treatment and therapy of a wide range of diseases and illnesses. This review summarizes studies highlighting the potential role of pomegranate in the prevention and treatment of diseases related to respiratory and digestive systems.

Keywords: pomegranate; cancer; antioxidant; respiratory; digestive; diseases

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1. Introduction

Phytotherapy is defined as the usage of plant-derived products in the treatment and prevention of diseases. Since the beginning of human civilization, medicinal plants have been used as pharmaceutics for the prevention and treatment of various diseases [1]. Medicinal plants play a major role in pharmaceutical industries as they contribute to the manufacturing of drugs [2]. Development of pharmaceutical drugs from plants reduces the use of synthetic antibiotics and increases life expectancy [3,4]. In the meantime, scientific interest in medicinal plants is increasing due to the high cost and side effects caused by allopathic drugs, in addition to the emergence of resistant microbial strains [5].

Pomegranate (*Punica granatum* L.) is derived from a deciduous tree in the Lythraceae family. According to reports, it first appeared in modern times in Iran and has since spread throughout the world. Since ancient times, it has been cultivated throughout the Mediterranean region and Northern India [6]. The pomegranate fruit is made of white to deep purple seeds that are enclosed in a white, spongy, astringent membrane, also known as pericarp, covered by a thick red skin and a crown-shaped calyx (Figure 1). This fruit is known to exhibit several biological properties, including antibacterial, anti-inflammatory, antioxidant, and anticancer activities [7,8]. The scientific studies on the health advantages of pomegranates that have been published over the past few decades demonstrate the scientific community's intense interest in the fruit's medicinal potential. Pomegranate has

been used in a variety of medical systems for the treatment and therapy of a wide range of diseases and illnesses. For instance, it was recommended as an antiparasitic agent and as a treatment for diarrhea and ulcers in ancient Indian medicinal systems [9,10]. Its importance in the treatment of diabetes has been recognized in another traditional system, the Unani system of medicine [11].

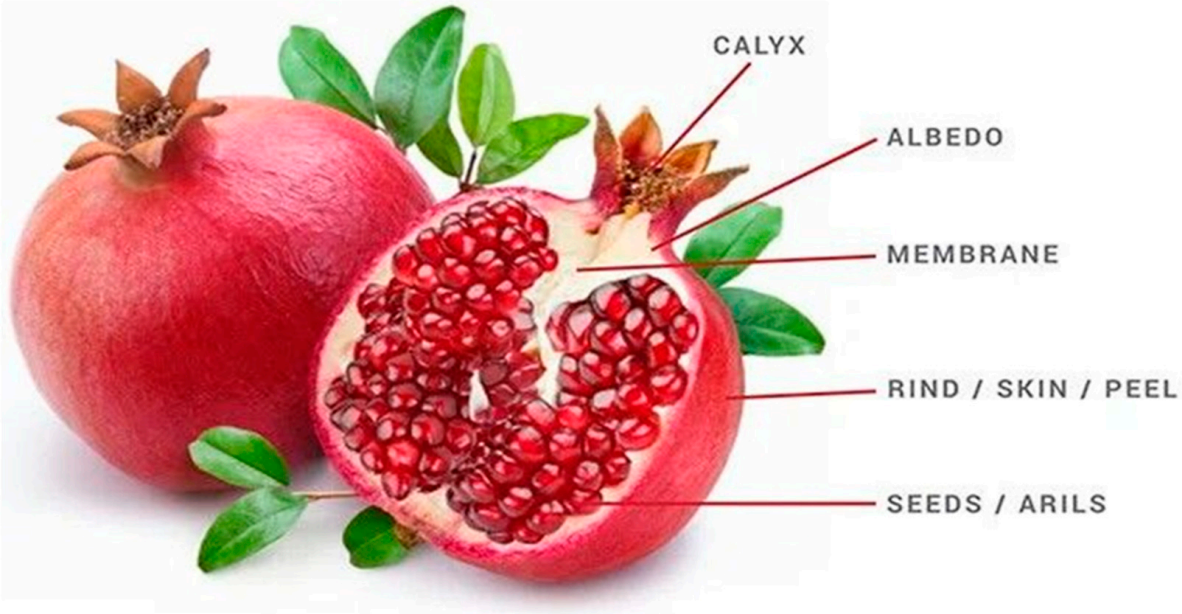

Figure 1. Pomegranate fruit parts.

In addition, pomegranate and its constituents have been shown in studies to effectively affect a number of signaling pathways involved in inflammation, cellular transformation, hyperproliferation, angiogenesis, and the start of tumorigenesis, as well as suppressing the later stages of tumorigenesis and metastasis [12,13]. Pomegranate peel has been shown to inhibit a wide range of pathogens, including viruses, bacteria, fungi, and mold [14]. It has a great therapeutic effect on chronic inflammation, particularly digestive tract inflammation like ulcerative colitis [15]. Furthermore, all waste parts of the pomegranate fruit, such as the peel and seeds, can be processed into value-added products with industrial, medicinal, and cosmetic value [16].

Chronic respiratory diseases are one of the leading causes of death globally. Victims of lung disorders frequently experience long-term difficulties, with one of the major causes being treatment side effects as well as psychosocial struggles [17]. Respiratory diseases are characterized by unrestricted cell proliferation and no single defined cause, but they are associated with several risk factors, including tobacco use, infection, radiation exposure, air pollution, obesity, and alcohol consumption. Several epigenetic/environmental agents have been identified as key players in the development and progression of such diseases [18,19]. Despite significant advances in treatment options, the number of cases and deaths continues to rise, and millions of people die from these diseases globally [20,21]. Moreover, gastrointestinal disorders are also common in the population and cause significant morbidity and healthcare costs [22]. These diseases occur from dietary components, microbes, alcohol, and other ingested materials, which target the digestive tract. External factors such as obesity, lack of physical exercise, and tobacco smoking increase the burden of gastrointestinal diseases [23].

The purpose of this review is to discuss the accumulated evidence indicating that pomegranate consumption has diverse biological actions and may be useful in the prevention and treatment of diseases related to the respiratory and digestive systems.

2. Pomegranate Chemical Composition

Interestingly, beside the pomegranate fruit itself, non-edible parts such as the bark, leaves, and roots of the pomegranate tree are also abundant in molecular components having therapeutic qualities [9–13,24]. Nearly half of the fruit's weight is made up of the pericarp, which is a rich source of bioactive compounds such phenolics, flavonoids, ellagitannins, and proanthocyanidin compounds. Along with complex polysaccharides, it also contains a number of minerals, primarily potassium (K), nitrogen (N), calcium (Ca), phosphorus (P), magnesium (Mg), and sodium (Na). A fruit's remaining 50% is made up of arils, which account for 40% of the fruit's weight, and seeds, which constitute the remaining 10% [25]. The high concentration of hydrolysable tannins (punicalagin, ellagic acid, etc.) and anthocyanins in pomegranate seeds gives them powerful anti-inflammatory and antioxidant characteristics. The seed coat has been shown to include a number of organic acids, including ascorbic acid, citric acid, etc., but the arils are mostly made up of pectin, water, and sugars, more precisely, fructose and glucose. The beneficial substances, phenolics, and flavonoids, especially anthocyanins, are abundant in arils [25]. Conjugated linolenic acid makes up the majority of the oil in pomegranate seeds [26]. Concerning the leaves, they are rich in tannins as well as mineral elements such as calcium, iron, potassium, and nitrogen. Their abundance depends mainly on the season and the maturity level of the plant [24,27,28]. In addition, the bark of the fruit and the roots are high in alkaloids, which give them medicinal properties [24]. The chemical structures of the main components are represented in Figure 2.

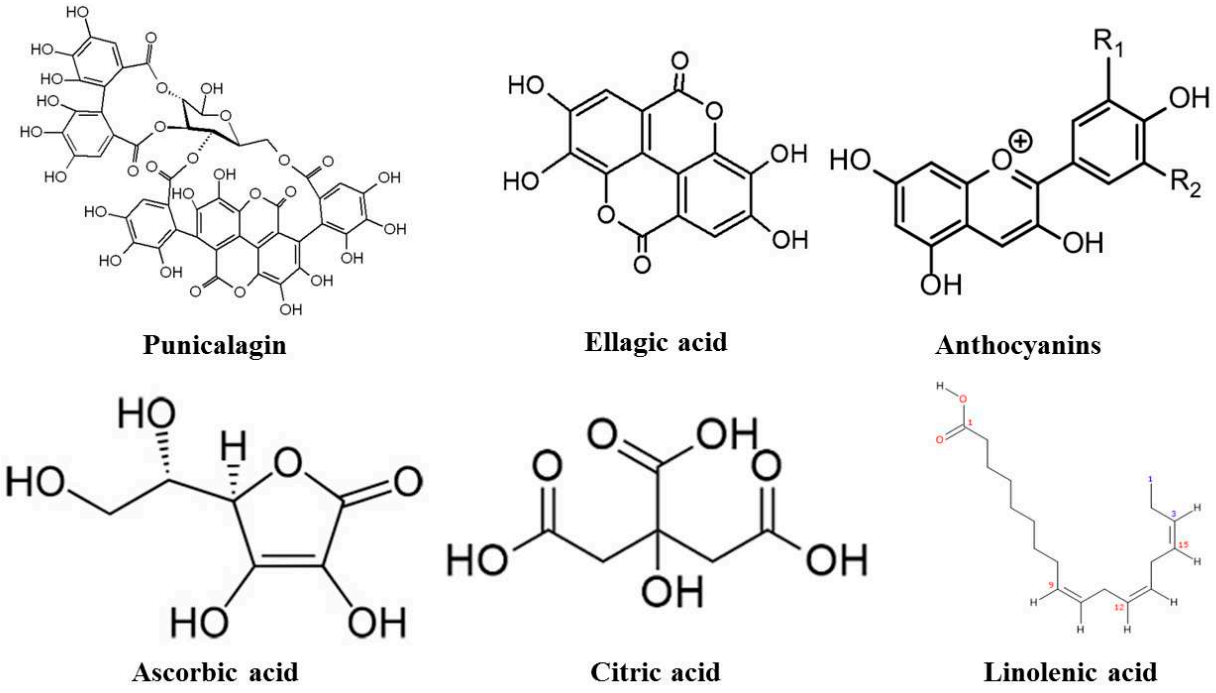

Figure 2. Pomegranate's constituents chemical structure.

3. Antioxidant Effect

Free radicals, also known as Reactive Oxygen Species (ROS), are produced as a result of radiation exposure, environmental contaminants, and drug metabolism by-products. More than one unpaired electron is present in free radicals, making them unstable and highly reactive with other species. In general, the human body's ongoing metabolic processes result in ROS, which specifically target carbohydrates, lipids, proteins, and nucleic acids [29]. Oxidative stress is an imbalance between the production and expression of ROS and the ability of a biological system to readily detoxify reactive intermediates or repair the resulting damage [30]. It is a chemical process that can result in free radicals and cascade events that could harm an organism's cells. These radicals are combated by

substances that are called antioxidants [29]. The latter are also known as "free radical scavengers" because they use radicals to create small reactive species. They can be divided into exogenous and endogenous antioxidants based on where they originate from. An antioxidant lowers the risk of developing a variety of diseases, including nephrotoxicity, cancer, diabetes, inflammation, liver disease, and neurological illnesses [31].

High levels of oxidative stress in target places in the organism, such as lung and gastrointestinal tract, contribute to a variety of pathological conditions. Aside from the skin, the lungs are the organs most exposed to ambient air. Therefore, they are readily attacked by inhaled toxins, gases, pollutants, pathogens, and oxidants, making them susceptible to exogenous oxidative damage. In addition, endogenous oxidants produced by pathophysiological processes in the lung also contribute to oxidative stress [32]. In addition, oxidative stress plays a role in the pathophysiology of several gastrointestinal illnesses. Despite the protective barrier provided by the mucosa, ingested materials and microbial pathogens can induce oxidative damage and gastrointestinal inflammation [33].

It is believed that dietary antioxidants may be able to prevent diseases brought on by oxidative stress. Pomegranate fruit is a rich source of multiple potent antioxidants. The antioxidant activity exhibited by pomegranate fruit makes it one of the major medicinal plants applied in the treatment of many diseases [34]. In comparison to the antioxidant activity of vitamin E, β-carotene, and ascorbic acid, pomegranate antioxidants are distinct due to combinations of a wide array of polyphenols, having a greater range of action against numerous types of free radicals [35]. Phenolic compounds found in such fruits are able to act as hydrogen donors and to chelate metal pro-oxidant transition metals such as iron and copper. Phenolic compounds can inhibit the oxidation of low-density lipoprotein (LDL) [36]. A study by Benchagra et al., 2021, revealed that pomegranate peel and aril phenolic extracts possess a significant free radical scavenging activity in a dose-dependent manner. Both extracts showed antioxidant activity through inhibiting copper ion–induced LDL-oxidation, preventing the degradation of other antioxidants such as α-tocopherol and promoting paraoxonase 1 (PON1) activity, which is an esterase that hydrolyzes oxidized lipids [37]. Moreover, the daily supplementation of pomegranate juice upregulates the expression and activity of PON1 in mice fed a high-fat diet [38]. A clinical case study showed that the consumption of pomegranate juice for 3 years by patients with carotid artery stenosis reduced LDL oxidation [39]. Pomegranate juice can reduce macrophage oxidative stress, free radicals, and lipid peroxidation [40]. Another study showed that the consumption of pomegranate juice attenuated lipid peroxidation, increased glutathione levels, and induced the upregulation of macrophage PON2 activity, thus reducing the macrophage oxidative stress [41]. Pomegraniin A, a pomegranate-derived polyphenol, strongly augmented SIRT3 promoter activity in Caco-2 colon carcinoma cells, leading to the enhancement of superoxide dismutase 2 (SOD2) and the reduction of ROS levels [42]. Interestingly, the polyphenolic compounds in pomegranate peel flour are released during the various gastrointestinal digestion steps and are bioaccessible to exert bioactivity after absorption, primarily as antioxidant compounds for the prevention of oxidative stress diseases [43]. Figure 3 summarizes the antioxidant mechanisms of pomegranate.

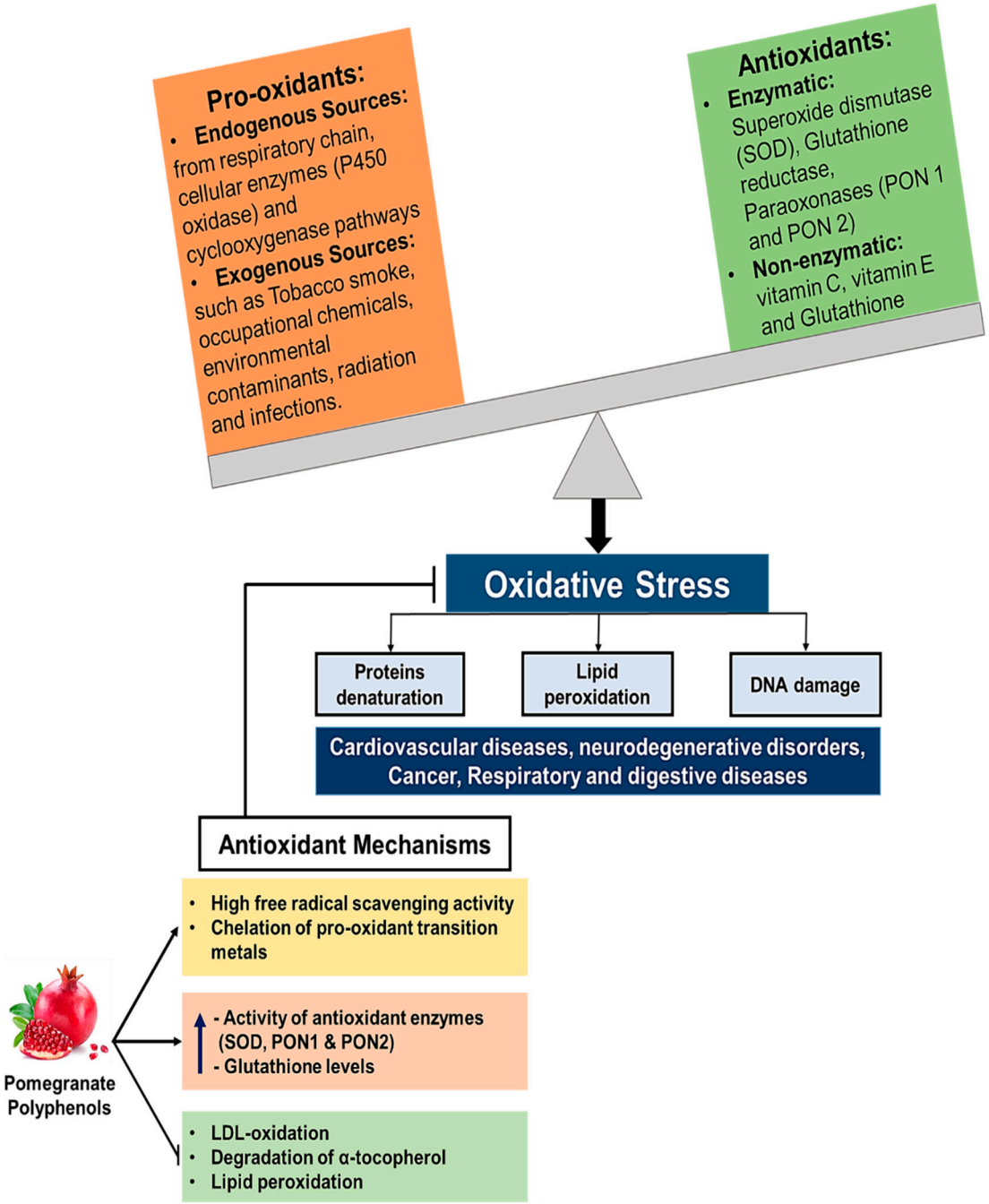

Figure 3. Antioxidant mechanisms of pomegranate.

4. Pomegranate in the Treatment of Respiratory Diseases

4.1. Pomegranate and Asthma

Asthma is a chronic condition in which the airways, due to inflammation, become narrow and swollen and are blocked by excess mucus. Treatment of asthma by inhalers can help control and minimize the symptoms, but their adverse effects ultimately limit their long-term use [44,45]. Studies have shown that pomegranate can play an effective medicinal role in asthma treatment. Eosinophils are involved in the development of asthma exacerbation and that IL-5 plays an important role in the activation and maturation of eosinophils [46]. Oliveira et al. revealed that the micro-encapsulated leaf extract from *Punica granatum* inhibited eosinophil recruitment to bronchoalveolar fluid and reduced the production of inflammatory cytokines such as IL-1b and IL-5 in the lungs of BALB/c mice

used as asthma models [47]. Another study revealed that tannins extracted from the flower buds of *P. granatum* display an anti-histaminic activity that could contribute to its role as a traditional treatment for asthma [48]. This antihistaminic activity may open the door for future research studies that could evaluate the cumulative effect between pomegranate extracts and other antihistaminic drugs. All these findings depicted the effective role of pomegranate as a therapy for asthma; more studies are needed for exploring the exact mechanism behind this therapeutic effect.

4.2. Pomegranate and COPD

Chronic obstructive pulmonary disease (COPD) is a respiratory disorder that causes airflow blockage and breathing-related problems. COPD is the third leading cause of mortality worldwide [49,50]. Cigarette smoking, indoor air pollution, and occupational dusts, fumes, and chemicals are important risk factors of COPD [51]. The exposure to cigarette smoke leads to severe oxidative damage to the lungs and to neutrophils recruitment via IL-1β and TNF-α. Neutrophils secrete proteases such as neutrophil elastase, caspases, and matrix metalloproteinases (MMPs), which break down the connective tissue in the lungs, resulting in emphysema [52]. Pomegranate has proven to be effective in treating COPD, even though the study done by Cerda et al. showed that pomegranate juice supplementation had no benefit in treating patients with stable COPD due to the metabolism of its polyphenols by the colonic microflora [53]. In fact, variations in polyphenol bioavailability and absorption could be possibly due to differences between individual and between species in gut microflora as well as differences in polyphenol structure [54,55]. Furthermore, in vitro research suggests that certain polyphenols in the colon may induce the production of conjugation enzymes, whereas in vivo research suggests that the composition of microbiota influences the capacity for producing enzymes required for conjugation [56,57]. External factors such as the food matrix in which polyphenols are consumed and health status can also influence polyphenol absorption efficiency. Age-related changes and metabolic disorders in the host have been shown to influence the distribution of intestinal microbiota, as well as the host's ability to metabolize specific polyphenols and the types of conjugated forms produced [58–60]

Other research studies had proven the effectiveness of pomegranate in treating COPD. Husari et al., 2016, proved that pomegranate juice supplementation in animal models exposed to cigarette smoke reduced the emphysematous changes and attenuated the expression of inflammatory mediators such as IL-1β, IL-6, and TNF-α [61]. Accordingly, pomegranate reduces apoptosis and oxidative stress induced by cigarette smoke exposure in the lungs. In vitro, pomegranate juice inhibited the devastating effects of cigarette smoke on cultured human alveolar cells [61]. In conclusion, these studies proved that pomegranate can act as a potential treatment for COPD as it attenuates the damaging effects of cigarette smoke on the lungs.

4.3. Pomegranate and Influenza

Influenza is a viral disease that affects the upper and lower respiratory tract. It is caused by a wide range of influenza viruses. Some of these viruses infect humans, while others are specific to other species [62,63]. Some medicinal plants have been identified for use in treating influenza due to the failure of some synthetic drugs because of side effects [64,65]. Pomegranate has been shown to possess a therapeutic effect against influenza virus infections. Pomegranate polyphenol juice extract showed anti-influenza properties, as it had inhibited the replication of influenza A virus in Madin-Darby canine kidney cells (MDCK). Punicalagin was found to have virucidal effects, being the most effective anti-viral component of polyphenol extract. Punicalagin suppressed viral RNA replication and blocked the agglutination of chicken RBCs by the virus. Moreover, combining oseltamivir, an anti-influenza drug, with pomegranate polyphenol extract showed a synergistic effect [66]. Another study revealed that pomegranate polyphenols inhibited influenza virus infectivity. Electron microscopic analysis revealed that viral inactivation by

pomegranate polyphenols was due to virion structural damage, with small changes in envelope glycoproteins [67]. Moradi et al. showed that the ethyl alcohol extract of pomegranate peel can suppress the replication of influenza A virus through inhibiting viral adsorption and internalization and viral RNA transcription [68,69]. Hence, pomegranate extracts must be further analyzed for therapeutic and prophylactic potential against influenza epidemics and pandemics.

4.4. Pomegranate and COVID-19

The extremely contagious respiratory illness COVID-19 is brought on by a new strain of coronavirus known as SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) [70]. Coronavirus causes infections in the respiratory tract ranging from mild colds to severe acute respiratory distress syndrome [71]. The interaction of SARS-CoV-2 spike (S) transmembrane glycoprotein with the angiotensin-converting enzyme 2 (ACE-2) receptor on host cells is an essential step for virus entry and onset of infection [72]. Attenuating the binding ability of S-glycoprotein to ACE-2 receptor was one of the primary targets for treating COVID-19 disease [73]. Pomegranate was shown to be potential candidate for possible therapeutic application against COVID-19. A recent study showed that pomegranate peel extract significantly blocked the binding of S-glycoprotein to ACE-2 receptor [74]. Another computational study showed that punicalagin and punicalin from pomegranate peel extract inhibited the SARS-CoV-2 internalization process [75]. Punicalagin alone or its combination with Zn particles inhibited the activity of SARS-CoV-2 3CL protease in vitro [76]. 3CL protease is indispensable for disease progression and viral replication, as it cleaves the viral polyprotein to give a single useful protein [77,78]. Other studies had also shown that some anthocyanins and hydrolysable tannins may inhibit viral replication via binding with catalytic dyad residues of 3CL protease [79–81]. Medicinal plants rich in anthocyanins and tannins, such as pomegranate, can be used as natural anti-COVID-19 therapeutic agents (Figure 4). Moreover, a clinical case study revealed that the consumption of fresh pomegranate juice showed prophylactic and therapeutic effects against COVID-19 [82]. These findings support the efficacy of *P. granatum* L. as a therapeutic drug in the treatment of COVID-19 (Figure 4).

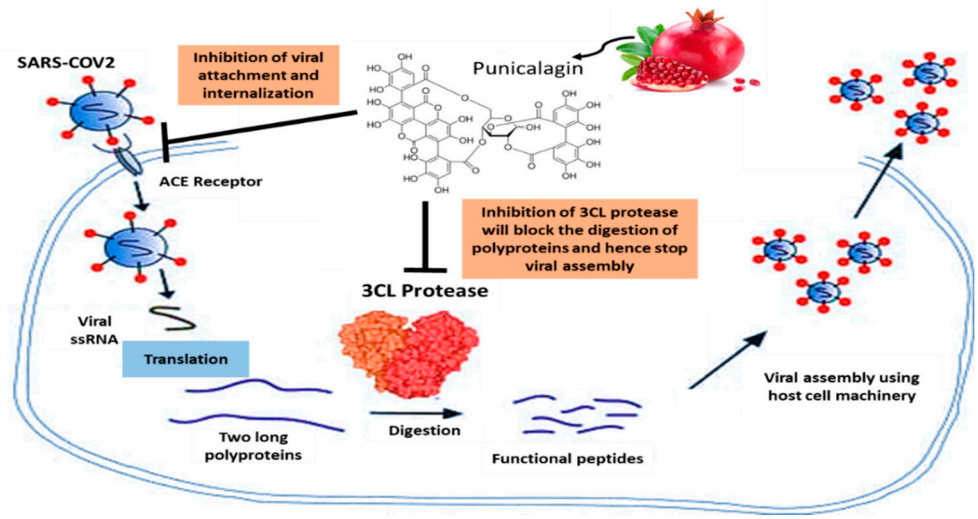

Figure 4. Pomegranate's role in COVID-19.

4.5. Pomegranate and Lung Cancer

Lung cancer remains the leading cause of cancer-related mortality worldwide. The year 2020 recorded 2.2 million new lung cancer cases, accounting for 11.4% of the global cancer burden [83,84]. Many technical and pharmacological advances have been made in the staging and treatment of lung cancer, with the approval of newly synthesized chemotherapeutic drugs that improve the prognosis of patients diagnosed with metastatic tumors [85]. Yet these drugs are linked to many undesired side effects, which can be avoided by their

substitution with natural products that have historically been invaluable as an origin of therapeutic agents [86,87]. Pomegranate has been shown to exhibit anti-cancerous effects against lung cancer in cell culture and in vivo studies. Punicalagin, an ellagitannin found in pomegranate peel, acts as an anti-proliferative agent on the A549 human lung carcinoma cell line. Punicalagin treatment induced apoptosis in A549 cells through mitochondria-mediated pathways without having any effect on normal lung fibroblast cells (MRC-5 cell line) [88]. Aqil et al. showed that punicalagin displays a strong anti-oxidant potential protecting against oxidative DNA damage and exhibits a strong anti-proliferative activity against lung cancer cells [89]. Punicalagin and its hydrolytic product (ellagic acid) showed cytotoxic effects on both human lung cancer cell lines A549 and H1299 [90]. Punicalagin inhibited STAT-3 translocation and accordingly induced apoptosis of A549 cells by inhibiting the expression of anti-apoptotic proteins (Bcl-2) and increasing the expression of the pro-apoptotic proteins (Bax, cytochrome C, caspase 9, and caspase 3) [91]. Another study investigated the anti-tumoral properties of pomegranate peel extract on A549 lung cancer cells. The authors showed that the peel extract reduced the cell viability, with a maximum growth inhibition of 80% at 250 µg/mL dose [92]. Moreover, the treatment of A549 cells with pomegranate fruit extract leads to a decrease in the viability of A549 cells with only minimal effects on normal human bronchial epithelial NHBE cells. Pomegranate fruit extract treatment leads to the G1 phase cell cycle arrest through the induction of WAF1/P21 and KIP1/P27, with consequent inhibition of cyclins D1, D2, and E as well as cyclin-dependent kinases cdk2, cdk4, and cdk6 [93]. In addition, treating A549 cells with pomegranate fruit extract resulted in the inhibition of MAPK and PI3K pathways as well as the NF-Kb pathway [93]. Yali Li et al. showed that pomegranate leaf extract exhibits anticancer effects through inhibiting the proliferation of A549 and H1299 non-small-cell lung carcinoma cell lines and mouse Lewis lung carcinoma cell line LL/2. Pomegranate leaf extract blocked the migration and invasion of H1299 cells via reducing the expression of metalloproteinases (MMPs), suggesting the effectiveness of pomegranate leaf extract in impairing metastasis [94]. Urothilin A, a major metabolite from pomegranate ellagitannins, was found to inhibit epithelial-to-mesenchymal transition (EMT) in lung cancer cells via decreasing the expression and activity of snail protein, an inducer of EMT [95]. Husari et al. showed that pomegranate juice supplementation to an animal model reduced the expression of HIF-1α and prevented the formation of lung nodules secondary to chronic cigarette smoke exposure, therefore decreasing the incidence of lung cancer [96]. These studies highlight the potential role of pomegranate fruit in the treatment of lung cancer (Figure 5).

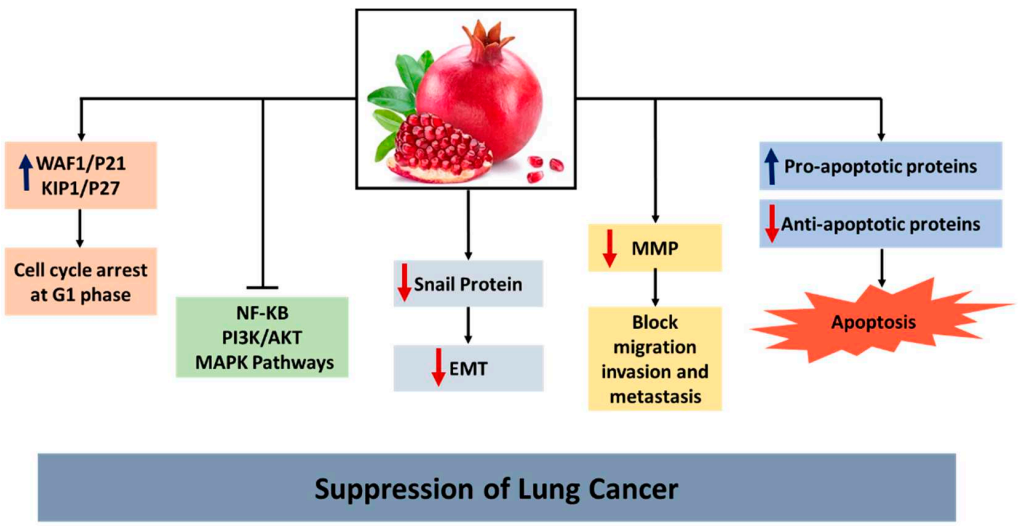

Figure 5. Pomegranate activity in lung cancer.

5. Pomegranate in the Treatment of Digestive Diseases

5.1. Pomegranate and Colorectal Cancer

As mentioned previously, pomegranate has an anti-cancer effect on various types of cancers, including colorectal cancer. The latter is one of the most common cancers diagnosed in both sexes, and it is characterized by uncontrolled proliferation of cells in the colon and rectum [97]. The ellagitannin urolithin A, one of the major constituents of pomegranate, has an important role in the hindering of colon cancer cell proliferation via cell cycle arrest and the hindering of MAPK (mitogen activated protein kinase) signaling [56]. Ellagitannins and urolithin derived from pomegranate juice were found to reduce the presence of CYP1 enzymes, which are involved in the conversion of inactive carcinogens into active carcinogenic chemicals in colon cancer [98]. In an experiment conducted on HT-29, a colon cancer cell line, the pomegranate's extracts were found to inhibit cell proliferation in a dose-dependent manner while excluding non-cancer cells. Pomegranate inhibited TNF-induced COX-2 protein expression, which is frequently expressed in cancer, as well decreased AKT activity, a protein involved in processes related to cell proliferation and survival [99]. Additionally, another study demonstrates how COX-2 selective inhibitor might decrease the proliferation of HT-29 cancer cells. Therefore, it is suggested that one key mechanism behind pomegranate juice's anti-proliferative effects on colon cancer is its ability to modulate COX-2 expression [90].

Furthermore, ellagitannin and urolithin were found to increase apoptosis in cell lines, resulting in a decrease in cell colony size. Both the lipid and aqueous pomegranate fractions appear to have selective apoptotic potential, downregulating cyclins A and B1 and upregulating cyclin E, resulting in S phase cell-cycle arrest and apoptosis via an intrinsic pathway mediated by cytochrome c release from mitochondria into the cytosol [24].Thus, by triggering apoptosis, both of these substances suppressed the growth of HT-29 cells in a time- and dose-dependent manner [98].

Pomegranate's chemopreventive activity against colon carcinogenesis has been linked to its antioxidant activity. By preventing azoxymethane-induced oxidative stress, pomegranate peel extract was able to decrease the genotoxicity and pre-malignant lesions caused by azoxymethane-induced colon cancer [100,101]. In addition, pomegranate extract significantly reduced tumor weight and hemoglobin concentrations in chick chorioallantoic membrane (CAM) implanted colon cancers; this suggests that pomegranate has anticancer properties, particularly through inhibition of angiogenesis [102]. In addition, the consumption of oil extracted from pomegranate seed was found to reduce the number of colonic adenocarcinomas [103] (Figure 6).

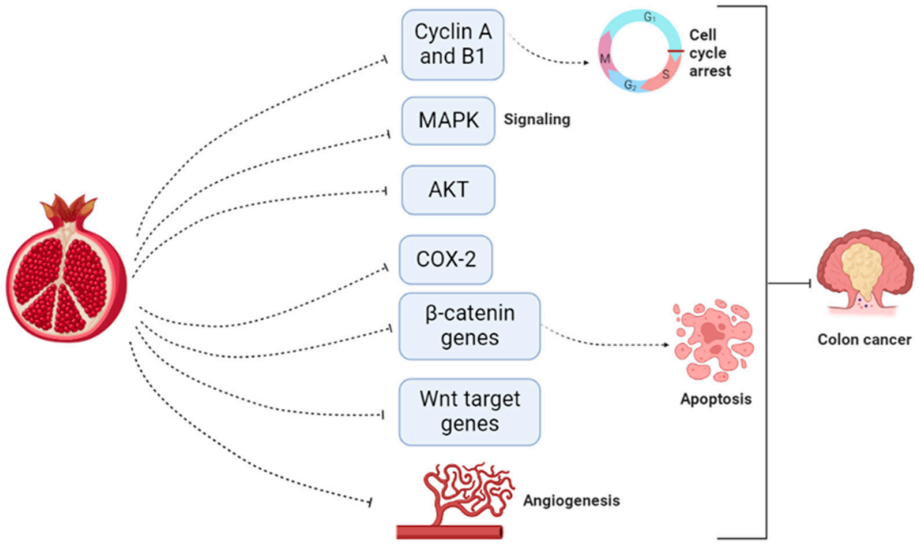

Figure 6. Pomegranate effect in colon cancer.

In vivo, several studies were also conducted to examine the anti-cancerous effect of the various components of pomegranate. Based on animal studies on rats that were affected with colon cancer, which caused an increase in antigens specific to colon cancer, it was discovered that pomegranate peel extracts caused a decrease in the cancer-specific parameters that were induced in mice. The in vivo study also suggested that pomegranate is effective in the treatment of colon cancer by inhibiting proliferation and increasing apoptosis, as evidenced the downregulation of β-catenin genes, which play a critical role in the progression of colon cancer [98,104,105]. In order to investigate the impact of pomegranate juice on colon cancer, its effect on aberrant cryptic foci (ACF) was examined more precisely. In fact, pomegranate juice significantly decreased the amount of colonic ACF in male rats by 91 percent. In addition, in rats fed pomegranate juice, it was discovered that the number of large crypts had significantly decreased, and these animals had few crypts/ACF that were visible. Another pathway is also included: the Wnt pathway. It contains a large number of secreted glycoproteins that regulate cell fate, differentiation, cell cycle, proliferation, and apoptosis [106]. The abnormal activation of Wnt signaling has been linked to colon cancer processes, and thus compounds that suppress this signaling pathway may play a role in cancer prevention and treatment [107]. For instance, rats that were induced to become carcinogenic showed an inhibition of the overexpression of many Wnt-target genes and of the tumor incidence when supplemented with pomegranate. Plus, both ellagic acid and urolithin A hindered the Wnt signaling with IC50 by 19 μg/mL and 9 μg/mL, respectively [106–109] (Figure 6). In conclusion, these studies indicate the beneficial role of pomegranate as an effective therapy for colon cancer.

5.2. Pomegranate and Intestinal Infectious Diseases

Pomegranate has been shown in a few studies to be effective in treating H. pylori infection. According to the size of the inhibitory zone in the disk diffusion method, which was comparable to the reference chemical metronidazole, pomegranate's methanolic peel extract demonstrated a significant anti-H. pylori activity in vitro [110]. In a different study, the pomegranate methanolic peel extract also demonstrated high activity against H. pylori strains when compared to other plant extracts [111]. The pomegranate ethanolic extract from the pericarp has also been shown to have strong anti-H pylori action [112].

Another example is that a susceptible C3H/HeJ mice strain that has a mutation in the TLR4 gene (a gene that codes for a protein involved in pathogen recognition and innate immunity stimulation) was treated with pomegranate peel extract and infected with *Citrobacter rodentium*. Pomegranate peel extract treatment did not prevent death, but it did shift the mortality curve, significantly extending survival time. Pomegranate peel extract treatment reduced the extent of *Citrobacter rodentium*-induced colon damage, which was associated with lower mortality and lower splenic colonization. Thus, pomegranate peel extract contains bioactive compounds that reduce the harmful effects of an in vivo infection with the model enteropathogenic bacteria, *Citrobacter rodentium* [113].

The intestinal epithelial cells may be directly impacted by harmful gut bacteria brought on by high fat diet or may create damaging metabolites that enable dysfunctional intestinal permeability and subsequent lipopolysaccharide leaking, with the colon releasing pro-inflammatory cytokines into the bloodstream. Pomegranate peel polyphenols reduced obesity brought on by a high fat diet in rats as well as the levels of circulating pro-inflammatory cytokines, colonic tissue damage, and colonic tight junction protein expression [114]. All these studies depicted the potentiality of pomegranate as a therapeutic drug for the treatment of intestinal infections.

5.3. Pomegranate and Ulcerative Colitis

Ulcerative colitis is a relapsing inflammatory disease that affects the mucosa of the large intestine, including the colon and rectum [115]. Chronic inflammation causes the mucosal lining of the colon to deteriorate and produces high levels of proinflammatory cytokines and inflammatory molecules, such as COX-2 and iNOS, which increase the risk

of cancer. As a result, interventions that reduce intestinal inflammation may reduce the risk of ulcerative colitis and consequently colon cancer [116].

In a certain study, rats were given either a control (CT) or a pomegranate beverage containing ellagic acid and ellagitannins before being subjected to three cycles of 3% dextran sodium sulfate (DSS)-induced colitis followed by a 2-week recovery period. Pomegranate reduced the Ki-67 proliferative index in the central and basal regions and protected against DSS-induced colon inflammation and ulceration [117].

In addition, after inducing colitis with 2,4-dinitrobenzenesulfonic acid (DNBS), pomegranate decoction, polysaccharides, and ellagitannins were ingested for 14 days. Repeated decoction treatment decreased visceral hypersensitivity in colitic animals at 7 and 14 days. Polysaccharides demonstrated similar efficacy, but at a lower potency. Ellagitannins at doses equivalent to decoction content were more effective in reducing the development of visceral pain. All three preparations reduced the overall number of mast cells, the number of degranulated mast cells, and the density of collagen fibers in the mucosal stroma in the colon 14 days after the damage, according to macroscopic and microscopic evaluations, and adjusted the inflammatory infiltrate as well as the number and distribution of crypts. As a result, pomegranate mesocarp preparations could be used in addition to traditional therapies to help relieve abdominal pain related to inflammatory bowel diseases [118].

Ulcers are caused by several factors, and ethanol is one of them. Ethanol directly affects the stomach mucosa and causes ulcers due to its ability to cause the necrosis and erosion of superficial gastric epithelial cells [119]. An in vivo study found that pomegranate fruit methanolic extract significantly reduced the ulcer index (UI) in ethanol-induced gastritis in rats. Additionally, intraluminal hemorrhage was prevented in rats given a high dose of pomegranate extract [120]. In rats with ethanol-induced stomach ulcers, it was shown that aqueous extract of pomegranate peel (AEP) exhibits a gastroprotective effect. Ingestion of alcohol and AEP at the same time dramatically reduced stomach lesions and UI [121].

Another cause of gastritis is nonsteroidal anti-inflammatory medications, NSAIDs. In many acute and chronic inflammatory disorders, NSAIDs such as acetylsalicylic acid are frequently used as analgesics. The secretion of mucus and bicarbonate, the hydrophobicity of the surface epithelium, and the blood flow across the mucosa are only a few of the defensive processes that acetylsalicylic acid disrupts in the stomach. In rats given acetylsalicylic acid, the pomegranate hydroalcoholic extract (methanol 70%) from powdered peel significantly reduced the ulceric index [120]. When tested at doses of 980 mg/kg and 490 mg/kg in another study, the hydroalcoholic extract (methanol:water 80:20) made from powdered pomegranate flowers inhibited ulceration by 83.9 percent and 73.8 percent, respectively, indicating that pomegranate flowers contain compounds with a dose-dependent gastric protective effect [122].

Gastric ischemia was induced for 20 min in rats, and this led the stomach mucosal blood flow to be significantly reduced, reaching 40–50% of basal levels. When these rats were pretreated with ellagic acid (EA), the elevated levels of lipid peroxidation brought on by ischemia/reperfusion were greatly decreased, with the inhibition being 78.3 percent [123]. In a different investigation, topical treatment with NH_4OH of an ischemic stomach resulted in a sustained decrease in the gastric potential difference and led to hemorrhagic injury. Preexposure of the mucosa to EA decreased the growth of gastric lesions brought on by the combination of NH_4OH and ischemia in a dose-dependent manner, with a substantial impact seen at concentrations above 3 mg/mL [122].

Furthermore, high levels of reactive oxidant species (ROS) produced by neutrophils and macrophages recruited in case of tissue inflammation, as well as a decreased antioxidant capacity of plasma, characterize inflammatory bowel diseases [123]. To demonstrate the antioxidant effect of pomegranate, its extract was administered, and the prevention of antioxidant depletion was shown [124]. In addition, a study was conducted on a model of colitis, which is distinguished by high levels of nitric oxide (NO) produced by iNOS induction. It is known that small amounts of NO have an anti-inflammatory effect in

endothelial cells, but the enzyme iNOS produces large amounts of NO during colon inflammation, which is involved in the development of the inflammation [125]. The findings of this study showed that both pomegranate extracts and UROA supplementation could suppress NO production by preventing iNOS induction [126].

A clinical study was conducted by Scaio et al., 2019, and the findings shed light on the possibility of a decrease in fecal calprotectin levels (a sensitive marker for inflammation in the gastrointestinal tract), after consuming pomegranate juice [127]. Another clinical study done by Kamali et al., 2015, had an objective to investigate the effect of the peel extract of pomegranate on the symptoms of patients with ulcers colitis. Patients were randomly assigned to either an aqueous extract of the *P. granatum* peel or a placebo for four weeks as a supplement to standard medications. The Lichtiger Colitis Activity Index (LCAI) was used to assess symptoms at baseline, week 4, and week 10 (follow-up). As a result, the pomegranate peel extract seemed to have a complementary effect with the medication, but further studies with bigger samples are required [128]. Altogether, these results confirm the potential effects of pomegranate in the management and treatment of ulcerative colitis.

5.4. Pomegranate and Diarrhea

One of the main symptoms of IBDs is diarrhea, which is mostly brought on by inflammation and increased intestinal transit, which reduces the absorption of water and electrolytes. The antidiarrheal activity of pomegranate in vivo was described in two trials. In a rat model, diarrhea brought on by castor oil treatment was reduced by intraperitoneal injection of an aqueous extract of pomegranate peels as well as oral administration of a crude methanolic extract from pomegranate rind. Intestinal weight and motility were decreased in a dose-dependent manner by pomegranate aqueous extract, which also inhibited ileum contractions [129]. On the other hand, pomegranate methanolic extract considerably reduced nitric oxide, a molecule involved in the diarrheal impact caused by castor oil, and exerted a strong antioxidant activity [130]. The secretion and gastrointestinal absorption of water and electrolytes can be impacted by the mineral composition of the digestive tract. Variations in the transit of gastrointestinal fluids and ions can cause digestive issues in cases of both mineral excess and deficiency In order to reverse the mineral content dysregulation during diarrhea, pomegranate extracts may be employed [131]. These studies support the potential effect of pomegranate in the prevention of diarrhea.

6. Pomegranate and Gut Microbiota

Numerous scientific studies have demonstrated the value of the human gut microbiota in promoting good health and preventing the development of numerous diseases. In reality, helpful bacterial species like Bifidobacterium and Lactobacillus operate as a crucial barrier against the proliferation of pathogenic strains, whose abundance has been linked to aging and cancer as well as chronic and acute bowel illnesses [132]. In fact, the preservation of physiological balance depends heavily on the regulation of gut microbiota by nutritional supplements and eating habits. Regarding this, a commercial pomegranate dietary supplement made of punicalagin and PomX, which was made from the extraction of juice production leftovers, showed a preferential toxicity toward intestine pathogenic bacteria as opposed to probiotic bacteria [133]. Particularly, PomX, punicalagin, and ellagic acid greatly reduced the growth of Clostridium and Staphylococcus aureus. Punicalagin also inhibited the growth of Escherichia coli and Pseudomonas aeruginosa [133]. The following are some potential explanations of the mechanisms underlying the antibacterial effect against harmful bacteria. In order for bacteria to survive, tannins may form stable complexes with proteins or physiological metal ions; polyphenols may lower the pH of the intestine, favoring the growth of probiotic bacteria rather than harmful bacteria [133]. Furthermore, by enhancing the quantity of favorable bacteria in the colon, pomegranate peel polyphenols balanced the gut microbiota imbalance brought on by the HFD [114]. Hence, the regulation of gut microbiota could be a novel benefit for pomegranate fruit on human health, as shown in Table 1.

Table 1. Summary of pomegranate's effect on respiratory and digestive diseases.

Diseases	Effect of Pomegranate
Asthma	Inhibits eosinophils recruitment to bronchoalveolar fluid Reduces the production of inflammatory cytokines (IL-1β and IL-5) Antihistaminic activity
COPD	Reduces emphysematous changes Decreases the expression of inflammatory mediators (IL-1β, IL-6 and TNFα) Reduces the oxidative stress induced by cigarette smoke
Influenza	Inhibits the replication of influenza A virus in MDCK cells Inhibits viral RNA replication Inhibits viral internalization and RNA transcription Exhibits a synergistic effect with the anti-influenza drug oseltamivir
COVID-19	Blocks the binding ability of S-glycoprotein to ACE-2 receptor Prevents SARS-CoV-2 internalization Inhibits 3CL protease Shows prophylactic and therapeutic effects in a clinical study
Lung cancer	Induces cell cycle arrest at G1 phase via increasing P21 and P27 protein expression Induces apoptosis through upregulation of pro-apoptotic proteins Decreases expression of snail protein and MMPs leading to inhibition of migration, invasion, and metastasis Inhibits MAPK, PI3K/AKT, and NF-κB pathways
Colon cancer	Hinders MAPK signaling Reduces the presence of CYP1 enzymes Inhibits TNF-induced COX-2 protein expression Decreases AKT activity Downregulates cyclins A and B1, resulting in S phase cell-cycle arrest and apoptosis Downregulates β-catenin genes and thus inhibits proliferation and increases apoptosis Hinders the Wnt signaling
Intestinal Infectious diseases	Reduces the harmful effects of infection Reduces obesity brought on by high fat diet in rats Reduces the levels of circulating pro-inflammatory cytokines, colonic tissue damage, and colonic tight junction protein expression
Ulcerative colitis	Reduces Ki-67 proliferative inde xReduces the overall number of mast cells, the number of degranulated mast cells, and the density of collagen fibers in the mucosal stroma in the colon Adjusts the inflammatory infiltrate, as well as the number and distribution of crypts Decreases the elevated levels of lipid peroxidation Decreases the growth of gastric lesions Suppresses NO production by preventing iNOS induction
Diarrhea	Decreases intestinal weight and motility Inhibits ileum contractions Reverse the mineral content dysregulation
Gut microbiota	Regulates the gut microbiota balance

7. Conclusions

A significant portion of the world's population uses traditional medicine, and many therapies including plant extracts or their active ingredients. According to recent research and financial investments, medicinal plants will presumably continue to be an essential part of the healthcare system. In this review, pomegranate was highlighted as a potential treatment option for respiratory and gastrointestinal disease. Pomegranate has gained popularity due to the abundant bioactive chemicals and the various secondary metabolites it contains. It has promising biological properties that have been linked to the numerous

elements that are found in edible and non-edible parts of the fruit, including antibacterial, anti-inflammatory, antioxidant, anticancer, and wound-healing activities. Biomedical research should be employed for the assessment of the safety, efficacy, and side effects of pomegranate's compounds. The application of these bioactive ingredients, especially punicalagin, in the pharmaceutical industry for the development of drugs is of great importance. Enhancing therapeutic effects can be accomplished by studying the cumulative and synergistic effects between pomegranate bioactive molecules and other known drugs. Additional carefully planned clinical trials are necessary to establish pomegranate's comprehensive clinical uses and therapeutic role.

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