From radish to raw papaya, 5 foods that can reverse fatty liver

Simple tips to reverse fatty liver

Fatty liver disease, often a result of poor diet and lifestyle choices, can lead to severe liver damage if left unchecked. However, incorporating specific foods into your diet can help reverse fatty liver and promote overall liver health. Here is a list of 5 powerful foods that can aid in this process. Take a look. (images courtesy: Canva)

shop similar look

2/8

Radish

Radishes are a powerhouse of nutrients and antioxidants that can support liver health. They contain high levels of fiber, which aids in digestion and helps flush out toxins from the liver. The enzymes present in radishes can also help prevent the buildup of fat in the liver. Regular consumption of radishes can assist in detoxifying the liver, reducing inflammation, and improving liver function.

Read More

shop similar look

3/8

Raw Papaya

Raw papaya is an excellent source of vitamins, enzymes, and fiber. The enzyme papain, found in raw papaya, promotes digestion and helps cleanse the liver by flushing out toxins. This enzyme also aids in breaking down proteins and fats, which can help prevent the accumulation of fat in the liver. Including raw

papaya in your diet can significantly enhance liver function and reduce the risk of fatty liver disease.

Read More

shop similar look

4/8

Amla (Indian Gooseberry)

Amla is renowned in Ayurvedic medicine for its numerous health benefits, particularly for the liver. It is rich in vitamin C and antioxidants, which help protect the liver from oxidative stress and damage. Amla also supports liver detoxification and can help reduce the buildup of fat in the liver. Consuming amla regularly,

whether in raw form, as juice, or as a supplement, can contribute to reversing fatty liver disease.

Read More

shop similar look

5/8

Turmeric

Turmeric, with its active compound curcumin, is well-known for its anti-inflammatory and antioxidant properties. Curcumin helps in reducing liver inflammation and oxidative stress, which are common in fatty liver disease. It also promotes the production of bile, which aids in digestion and the breakdown of fats. Including

turmeric in your diet, either as a spice or in supplement form, can support liver health and assist in reversing fatty liver disease.

Read More

shop similar look

6/8

Dandelion

Dandelion is a lesser-known but highly effective herb for liver health. It acts as a natural diuretic, helping to flush out toxins and excess fat from the liver. Dandelion also contains compounds that stimulate bile production, aiding in digestion and fat metabolism. Drinking dandelion tea or incorporating dandelion greens into

your diet can significantly benefit liver function and help reverse fatty liver disease.

Read More

shop similar look

7/8

Additional tips for liver health

Along with these five foods, it is crucial to maintain a balanced diet rich in fruits, vegetables, whole grains, and lean proteins. Avoiding processed foods, excessive sugar, and unhealthy fats can also help prevent and reverse fatty liver disease. Also it is important to drink plenty of water, as it helps in flushing out toxins from the liver and supports overall liver function. Physical

activity helps in reducing liver fat and improving overall health. Aim for at least 30 minutes of moderate exercise most days of the week. One should also make sure to limit alcohol intake, as excessive alcohol consumption can lead to liver damage. Limiting or avoiding alcohol can significantly improve liver health. There are some medications also that can affect liver function. Always consult with a healthcare provider before starting or stopping any medication.

biology

MDPI

Review

Beneficial Role of *Carica papaya* Extracts and Phytochemicals on Oxidative Stress and Related Diseases: A Mini Review

Yew Rong Kong [1,†], Yong Xin Jong [1,†], Manisha Balakrishnan [1,†], Zhui Ken Bok [1,†], Janice Kwan Kah Weng [1,†], Kai Ching Tay [1,†], Bey Hing Goh [1,2], Yong Sze Ong [1], Kok Gan Chan [3,4,*], Learn Han Lee [5,*] and Kooi Yeong Khaw [1,*]

1 Biofunctional Molecule Exploratory Research Group (BMEX), School of Pharmacy, Monash University Malaysia, Bandar Sunway 47500, Malaysia; ykon0007@student.monash.edu (Y.R.K.); yjon0001@student.monash.edu (Y.X.J.); mbal0001@student.monash.edu (M.B.); zbok0001@student.monash.edu (Z.K.B.); janicekwan97@gmail.com (J.K.K.W.); kctayyy@gmail.com (K.C.T.); goh.bey.hing@monash.edu (B.H.G.); Ong.YongSze@monash.edu (Y.S.O.)
2 College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China
3 Division of Genetics and Molecular Biology, Faculty of Science, Institute of Biological Sciences, University of Malaya, Kuala Lumpur 50603, Malaysia
4 Institute of Marine Sciences, Shantou University, Shantou 515063, China
5 Novel Bacteria and Drug Discovery Research Group (NBDD), Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway 47500, Malaysia
* Correspondence: kokgan@um.edu.my (K.G.C.); learn.han.lee@monash.edu (L.H.L.); khaw.kooiyeong@monash.edu (K.Y.K.)
† Equal contribution.

Simple Summary: This review highlights the medicinal benefits of a natural remedy, the *Carica papaya* extracts and its phytochemicals. In this review, the potential of *Carica papaya* against various conditions, including cancer, inflammation, aging, healing of the skin, and lifelong diseases has been summarized and discussed. In short, more research and development should focus on this natural remedy that can potentially act as a prophylaxis against chronic diseases.

Abstract: Oxidative stress is a result of disruption in the balance between antioxidants and pro-oxidants in which subsequently impacting on redox signaling, causing cell and tissue damages. It leads to a range of medical conditions including inflammation, skin aging, impaired wound healing, chronic diseases and cancers but these conditions can be managed properly with the aid of antioxidants. This review features various studies to provide an overview on how *Carica papaya* help counteract oxidative stress via various mechanisms of action closely related to its antioxidant properties and eventually improving the management of various oxidative stress-related health conditions. *Carica papaya* is a topical plant species discovered to contain high amounts of natural antioxidants that can usually be found in their leaves, fruits and seeds. It contains various chemical compounds demonstrate significant antioxidant properties including caffeic acid, myricetin, rutin, quercetin, α-tocopherol, papain, benzyl isothiocyanate (BiTC), and kaempferol. Therefore, it can counteract pro-oxidants via a number of signaling pathways that either promote the expression of antioxidant enzymes or reduce ROS production. These signaling pathways activate the antioxidant defense mechanisms that protect the body against both intrinsic and extrinsic oxidative stress. To conclude, *Carica papaya* can be incorporated into medications or supplements to help manage the health conditions driven by oxidative stress and further studies are needed to investigate the potential of its chemical components to manage various chronic diseases.

Keywords: oxidative stress; antioxidant; *Carica papaya*; inflammation; diabetes; cancer; aging; wound healing; periodontal disease; Alzheimer's disease

Citation: Kong, Y.R.; Jong, Y.X.; Balakrishnan, M.; Bok, Z.K.; Weng, J.K.K.; Tay, K.C.; Goh, B.H.; Ong, Y.S.; Chan, K.G.; Lee, L.H.; et al. Beneficial Role of *Carica papaya* Extracts and Phytochemicals on Oxidative Stress and Related Diseases: A Mini Review. *Biology* **2021**, *10*, 287. https://doi.org/10.3390/biology10040287

Academic Editor: Francisco Les

Received: 8 March 2021
Accepted: 30 March 2021
Published: 1 April 2021

1. Introduction

Oxidative stress is a natural phenomenon, resulting from the disruption of the redox equilibrium due to the amount of pro-oxidants outweighing antioxidants, which can eventually result in cell or tissue damage. As the name suggests, either oxidative stress can be induced by the presence of a high amount of pro-oxidants or the incompetence of antioxidant defense mechanism in the human body. In normal circumstances, human body is capable of scavenging free radicals, inhibiting the generation of oxidative stress with the help of several antioxidant enzymes, including glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT). Among various pro-oxidants, those free radicals that contain oxygen are known as reactive oxygen species (ROS), and ROS are considered as the secondary products of aerobic metabolism. Examples of ROS include singlet oxygen, hydroxyl radicals, superoxide radicals, and hydrogen peroxide. Sources of free radicals include diet, environment, and sunlight exposure and their accumulation can lead to oxidative stress and tissue injury, consequently leading to aging of the skin and medical conditions, including Alzheimer's disease (AD), rheumatoid arthritis, asthma, atherosclerosis, and cancers [1,2]. Various researches have been conducted to investigate the pathophysiology of diseases related to oxidative stress and the benefits of antioxidants in treating those diseases. Antioxidants can be found abundantly in plants. An example of antioxidant-rich plant is the *Carica papaya* L., which is a flowering and dicotyledonous plant, classified as violales order, *Caricaceae* family, *Carica* L. genus, and papaya species [3]. The *Carica papaya* L. has a single hollow light greenish to brownish stem with scarring, bearing big leaves and big oval fruits. Besides, this plant is cultivated in countries, such as Malaysia, Brazil, South America, Australia, and Indonesia, which are located near to the equator. The *Carica papaya* L. plant is known as many different names, such as kepaya, paw paw, or tapaya, based on its geographical distribution. In fact, this plant is acclaimed for an array of medicinal values from each part of the plant including fruit, roots, leaves, and seeds of the plant. Therefore it has been used as a traditional treatment regimen for various diseases [4]. Some of the medicinal properties of the plant can be explained by its antioxidative property, which confer protection on the cells from being harmed by oxidative stress [5]. Papain is the most widely exploited proteolytic enzyme from the *Carica papaya* L. and it has been used to help with meat tenderization and digestion. It is worth to note that papain exhibited great potential as a medication [4], as it is suggested to exhibit drug-like properties for atherosclerosis and associated conditions, which involve monocyte-platelet aggregate (MPA)-regulated inflammation [6]. Relevant and significant studies have been conducted to evaluate the benefits of the *Carica papaya* extracts and chemical constituents. This review aims to gather and summarize the research findings linking the *Carica papaya* to its antioxidant properties and the utilization of this natural resource as a pharmaceutical, cosmeceutical, and nutraceutical products.

2. Methods

All literature was retrieved from databases (PubMed, Semantic Scholar, Web of Science, WorldWideScience, and Embase) using search terms, including "*Carica papaya*", "inflammation", "cancer", "Alzheimer's Disease", "diabetes", "aging", "wound healing" and "oxidative stress". Literatures published from 2000 to 2020, investigating the benefits of the *Carica papaya* plant towards various conditions, were included. Literatures that were not related to oxidative stress mechanisms were excluded. Literatures selected were categorized based on related conditions including inflammation, cancer, skin aging, wound healing, diabetes, periodontal diseases, and Alzheimer's disease (AD). The mechanisms of action of the *Carica papaya* towards each condition were also presented in tables in the respective sections.

3. *Carica papaya* Counteracts Oxidative Stress in Inflammation, Skin Aging, and Healing, Chronic Diseases, and Cancers

Oxidative stress occurs due to excessive ROS production, which will cause oxidative damage to tissues. Consequence effects of oxidative stress has known to cause inflammation, leading to the development of various health conditions, including AD, rheumatoid disease, cardiovascular diseases (CVDs), cancers, cataracts, as well as cosmetic issues, such as the formation of wrinkles and loss of elasticity of the skin [7,8]. Figure 1 provides an overview of the role of oxidative stress in these conditions.

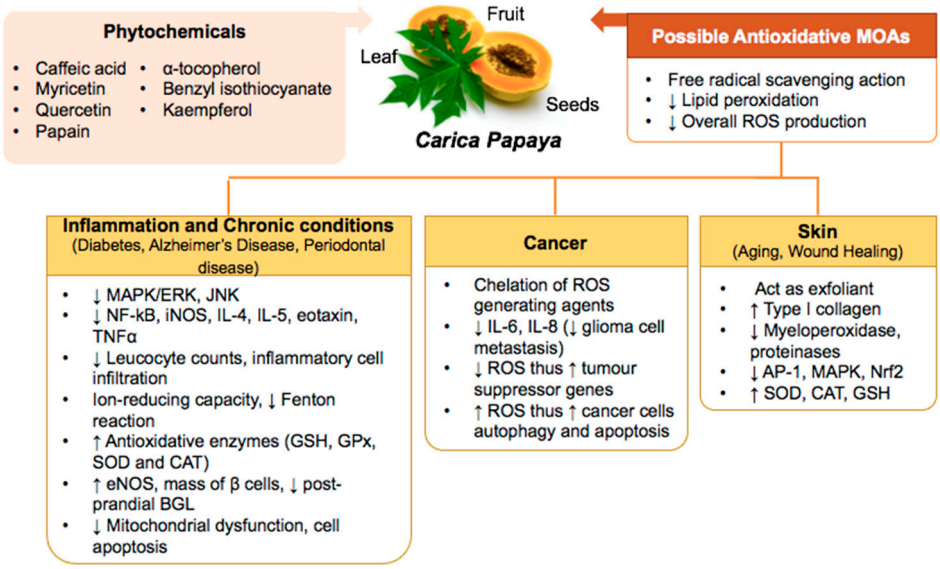

Figure 1. Role of oxidative stress in different medical conditions.

3.1. Inflammation

Inflammation is a complicated pathway of the body's own protective mechanism against pathogens, which is associated with symptoms such as pain, swelling, and redness due to the release of a mediator "prostaglandin" [9]. This defensive action can be divided into innate and adaptive responses [10]. In short, the pathogenesis of inflammation starts with tissue injury, which causes infiltration and activation of macrophages and relevant antigen-presenting cells (APCs). This causes the release of proinflammatory cytokines such as tumour necrosis factor-α (TNF-α) and interleukins (ILs). Cytokines stimulate the release of chemokines, which further recruit and activate lymphocytes and leukocytes. ROS are produced to eliminate invaders whereby activates Nuclear factor kappa-B (NF-κB). NF-κB is a transcription factor and plays a role in inducing inducible nitric oxide synthase (iNOS) activity and, thus, nitric oxide (NO) production. Excessive ROS upregulated prostaglandin E2 (PGE2) synthesis and, hence, cyclooxygenase-2 (COX-2) expression, which eventually leads to oxidative stress that causes tissue damage and worsens inflammation [11–13].

Another study further suggested that oxidative stress and inflammation are interrelated as oxidative stress resulting from high ROS can precipitate the formation of inflammation by increasing the gene expression coding for inflammatory proteins, including NF-κB, peroxisome proliferator activator receptor gamma (PPAR-γ), and activator protein 1 (AP-1). Consequently, inflammatory chemokines and cytokines are produced to induce inflammation. On the other hand, inflammation can increase ROS production via several signaling cascades. Polymorphonuclear neutrophils (PMN) is an immune cell that is largely involved in inflammatory processes. During inflammation, they congregate the gp91-phox, which is a catalytic subunit of NADPH oxidase 2 (NOX) and generate more ROS, including hydroxyl radical, superoxide anion, and hypochlorous acid, thereby enhance inflammation through mitogen-activated protein kinase (MAPK), protein kinase C (PKC), and c-Jun-N-terminal kinase (JNK) pathways [14]. Activation of these signaling cascades lead to production

of more inflammatory chemokines and cytokines. Therefore, this forms a vicious cycle leading to chronic inflammation and eventually a range of medical conditions, including cardiovascular diseases, neurodegenerative diseases, and cancers [12,14].

Table 1 shows anti-inflammatory activities of *Carica papaya*. Different parts of *Carica papaya* possess anti-inflammatory effects. Aqueous extract of *Carica papaya* seeds significantly reduced NO radical by 69.4% in a cell free assay in vitro. Meanwhile, the aqueous extract at a concentration of 150 µg/mL inhibited the release of lysosomal enzymes and stabilized human red blood cell membrane by 22.7%. On the contrary, the extract exhibited least potent hydroxyl radical scavenging action (69.1%) at a concentration 95 mg/mL and reducing power at a concentration of 20 mg/mL [15]. Meanwhile, Aruoma and colleagues demonstrated that fermented papaya preparation (FPP) inhibited H_2O_2-induced phosphorylation of Akt and p38, as well as downregulating MAPK pathway [16]. An in vivo study showed that *Carica papaya* leaf extract at a dose of 1.32 µg/mL demonstrated immune modulation properties [17].

Table 1. Anti-inflammation activities of *Carica papaya*.

Part of the Plant	Extract	Type of Experiment	Results	Reference
Seed	Aqueous extract	In vitro cell free model In vitro HRBC assay	Aqueous extract of papaya seeds at 20 µg/mL decreased NO radical by 69.4%, comparable to ascorbic acid.	[15]
			Aqueous extract of papaya seeds at 150 µg/mL inhibited the release of lysosomal enzyme by 22.7%.	
Leaf	Leaf extract	In vitro animal model	Leaf extract at 1.32 µg/mL enhanced adaptive immune response by upregulated TLR-7 and TLR-9 expressions.	[17]
Fruit (ripe, unripe fruit, peel, seed, pulp)	Aqueous extract	In vitro ROS assay	Unripe peel (69.7%) and seed (79.1%) extract at 2mg/mL showed ROS scavenging activity of 69.7 and 79.1% at 2 mg dry weight/mL.	[18]
		In vitro antioxidant enzyme assay	Aqueous extract of papaya unripe peel at 2 mg dry weight/mL increased SOD activity by 21.9%.	
		In vitro protein carbonyl assay	Aqueous extract reduced oxidative damage by lowered protein carbonyl production for ripe seed (60.4%) and ripe peel (57.6%) extract at 0.1 and 2 mg/mL.	
		In vitro inflammatory cytokines assay	The extracts augmented IL-10 levels at a low concentration of 0.1 mg/mL. Seed extracts exerted highest increment in IL-10 secretory level (+140.1%), followed by peel and pulp extracts. Seed extracts at 0.1 mg dry weight/mL exerted increment in IL-10 secretory level (+140.1%).	
			Aqueous extract of papaya seeds at 2 mg dry weight/mL down regulated IL-6 by 37.8%.	
			Unripe extracts at 2 mg/mL showed inhibitory activity against TNF-α with 71.2% for pulp extract, 62.7% for peel and 65.3% for seed extract.	

Table 1. *Cont.*

Part of the Plant	Extract	Type of Experiment	Results	Reference
Fruit (Flesh)	Juice	In vitro animal model	Papaya juice downregulated the elevated serum IL-6 (217.6 vs. 28.3 pg/dL) and MDA (3.2 vs.1.4 pg/dL) in high fat diets treated rats. Papaya juice affected serum SOD of the high fat treated rat by increased serum SOD (30.41 U/L).	[19]
Leaf	Ethanol extract	In vitro animal model	Ethanol extract of papaya leaves at 200 mg/kg reduced paw edema (2.6 mm) and inhibited granuloma formation (0.2 g).	[20]

Abbreviation: NO, nitric oxide; HRBC, human red blood cell; TLR, toll-like receptors, MDA, serum malondialdehyde.

Somanah and co-workers revealed that papaya extracts at a dose of 2 mg/mL showed protective effects through attenuated ROS production and pro-inflammatory cytokines secretion of interleukin-6 (IL-6) and TNF-α as well as upregulating antioxidant enzymes activities [18]. Another in vivo study showed that papaya juice demonstrated anti-obesity properties by reducing obesity markers, inflammation and oxidative stress in high-fat diet rats by upregulating SOD levels, attenuated serum malondialdehyde (MDA), PPAR-γ, lipid peroxidation, and ROS production at a treatment dose of 1 mL per 100 g of body weight [19].

The anti-inflammatory effect of *Carica papaya* was further investigated on various in vivo experimental studies. For instance, ethanolic extract of *Carica papaya* leaves was found to reduce paw edema induced by carrageenan, granuloma formation, as well as inflammation in formaldehyde-induced arthritis rats at doses of 25–200 mg/kg [20]. Methanolic extract of *Carica papaya* seeds at dosage range of 50 to 200 mg/kg exhibited anti-inflammation activities in egg albumin induced inflammation on Wistar albino rats [21]. Similarly, the aqueous extract of *Carica papaya* seeds at a dose of 400 mg/kg showed anti-inflammatory in carrageenan and formalin induced pedal edema rats [22].

High phenolic and flavonoid content in papaya seed extracts were proposed to act as free radical scavengers and metal ion chelators [15]. Phytochemicals including tocopherols and quercetin are showed to enhance AMP-activated protein kinase (AMPK) activation, as well as the inhibition of COX-2 expression [17]. In addition, a range of phytochemicals with great strength of anti-inflammatory effect, such as benzyl isothiocyanate (BiTC), β-carotene, lycopene, and vitamin C could be found in various parts of papaya fruits, in either pulp or seeds. These phytochemicals were proven to inhibit pro-inflammatory cytokines including TNF-α, IL-6 and monocyte chemoattractant protein-1 (MCP-1) [18,19]. In addition, polyphenols within *Carica papaya* could act as free radical scavenger and at the same time exerting its effects in upregulating the antioxidant enzymes activities [18].

3.2. Diabetes

Diabetes is a chronic disease, predominantly due to the insulin resistance or insulin insufficiency phenomenon, which leads to elevation of blood glucose level, a condition known as hyperglycemia [23]. Uncontrolled diabetes can lead to various macro and microvascular complications in which ultimately affect the quality of life of diabetes patients. It has been shown that oxidative stress plays an important role in diabetes and its progression [24]. There are tremendous amount of evidences revealed that uncontrolled hyperglycemia might induce oxidative stress by promoting ROS production and weakening antioxidant defenses via several mechanisms, including inducing lipid peroxidation of low-density lipoprotein (LDL), glycation of proteins, and glucose oxidation. Non-enzymatic interaction of glucose with proteins generates advanced glycation end products (AGEs), and increases nitric oxide (NO). Excessive free radicals can cause dysfunction of β-cells of the islets of Langerhans of pancreas and lead to complications. Thus, these findings support the role of antioxidants in diabetic control [25,26]. Table 2 shows anti-diabetic activities

of *Carica papaya*. Agada and co-workers demonstrated that the ethyl acetate extract of *Carica papaya* seeds significantly reduced postprandial glucose levels in streptozotocin-induced diabetic rats. Along with in vivo study, ethyl acetate showed α-glucosidase and α-amylase enzyme inhibitory effect and antioxidant activities in vitro, whereas hexane extract exhibited slightly more potent enzyme inhibitory activities [27].

Table 2. Anti-diabetes activities of *Carica papaya.*

Part of the Plant	Extract	Type of Experiment	Results	Reference
Seed	Hexane extract & ethyl acetate extract	In vitro DPPH radical scavenging assay	Hexane extract possessed DPPH radical scavenging activity with IC_{50} = 41.5 mg/mL.	[27]
		In vitro TBA method	Hexane extract demonstrated TBA scavenging activity with IC_{50} = 38.2 mg/mL.	
		In vitro α-glucosidase inhibition	Hexane extract displayed α-glucosidase enzyme inhibitory activity with IC_{50} = 75.78 mg/mL.	
			Ethyl acetate extract exhibited α-glucosidase enzyme inhibitory activity with IC_{50} = 77.41 mg/mL.	
		In vitro α-amylase inhibition	Hexane extract demonstrated α-amylase inhibitory activity with IC_{50} = 76.96 mg/mL.	
			Ethyl acetate extract displayed α-amylase inhibitory activity with IC_{50} = 79.18 mg/mL.	
		In vitro FRAP assay	Ethyl acetate extract displayed FRAP inhibitory activity with IC_{50} = 38.75 mg/mL.	
		In vitro animal model	Ethyl acetate extract at 500 mg/kg/body weight significantly decreased the blood glucose level of the diabetic rats to approximately 120 mmol/L over 120 min comparable with standard drug, acarbose.	
-	FPP	In vitro analysis	FPP at concentration 50 µg/mL increased inner and outer platelet membrane fluidity, displayed by a decrease of ~0.015 r in DPH anisotropy and ~0.02 r in TMA-DPH anisotropy. FPP increased Naþ/Kþ-ATPase activity by ~0.5 µmol Pi/mg prot/h.-FPP improved platelet function in vitro and this might help preventing diabetic complications. FPP also slightly increased TAC by ~5 nmol/µL and SOD activity by ~0.5 units/µL. FPP at 50 µg/mL lowered lipid peroxidation.	[28]
-	FPP®	Human trial	FPP significantly improved liver sensitivity to insulin, which was indicated by decreased circulating AST and ALT. FPP scavenged NO and hydroxyl radicals and displayed an increased in total antioxidant status.	[29]

Table 2. *Cont.*

Part of the Plant	Extract	Type of Experiment	Results	Reference
-	FPP	In vitro DPPH radical scavenging assay	FPP displayed DPPH scavenging with AA_{50} = 55.69 mg/mL.	[30]
		In vitro $ABTS^+$ scavenging assay	FPP demonstrated $ABTS^+$ scavenging action with AA_{50} = 14.56 mg/mL.	
		In vitro AAPH-induced lipid oxidation inhibition	FPP inhibited AAPH-induced lipid oxidation with AA_{50} = 68.06 mg/mL.	
		In vitro O_2^- scavenging assay	FPP showed O_2^- scavenging action with AA_{50} = 88.70 mg/mL.	
		In vitro •OH scavenging assay	FPP showed hydroxyl radical scavenging activity with AA_{50} = 4.13 mg/mL.	
		Human trial	FPP at a dose of 6g/day showed an increase of 4.9% and 5.7% in TAS for male and female respectively after 14-week consumption at 6g/day. FPP decreased protein carbonyl level by 1.9% in males and 9.7% in females after a 14-week FPP ingestion. FPP delayed red blood cell hemolysis.	
Seed, flesh and peel of unripe fruit	Aqueous extract	In vitro α-amylase inhibition In vitro α-glucosidase inhibition In vitro lipid peroxidation assay In vitro NO scavenging assay	Aqueous extract inhibited α-glucosidase and α-amylase activities with IC_{50} of 1.76 mg/mL and IC_{50}: 0.87 mg/mL. At a concentration of 7.5 mg/mL, the extract also displayed the highest NO radical scavenging activity (52.5%).	[31]
Leaf	Chloroform extract	In vitro animal model	The chloroform extract at a dose of 31 mg/kg/day significantly increased islet area by 16,842.2 μm^2 by stimulating regeneration of β-cells of islet of Langerhans.	[32]
			The extract successfully decreased fasting glucose levels by 222.3 mg/dL in diabetic group in vivo.	
Leaf	Aqueous extract	In vitro animal model	Aqueous extract at a dose of 3 g/100 mL decreased blood glucose levels in diabetic rats by 184 mg/dL. Aqueous extract at a dose of 1.5 g/100 mL preserved Islet cell size in diabetic rats. Aqueous extract increased NO levels by 17.39 μM and hence reduced ROS production.	[33]

Abbreviation: DPPH, 2,2-diphenyl-1-picryl-hydrazyl-hydrate; TBA, thiobarbituric acid; FPP, fermented papaya preparation; TAC, total antioxidant capacity; SOD, superoxide dismutase; AST, aspartate transaminase; ALT, alanine aminotransferase; NO, nitric oxide. Footnote: IC_{50} = concentration needed for 50% inhibition; AA_{50} = concentration needed to achieve 50% antioxidant activity.

Carica papaya FPP extract showed protective effect against diabetic complications such as atherosclerotic plaque formation, upregulated SOD level and ameliorated lipid peroxidation at a concentration of 50 μg/mL. In addition, increasing platelet membrane fluidity of diabetic patients and preventing chronic hyperglycemia-induced platelet malfunction [28]. Likewise, Somanah and colleagues conducted a study on the impact of short-term supplementation of fermented papaya preparation (FPP) on the biomarkers of diabetes mellitus. The randomized controlled trial showed that daily consumption of 6 g of FPP for a period

of 14 weeks enhanced the antioxidant status of the subjects and improved general health status of several organs that were potentially at risk of damage from diabetes. In addition, the FPP extract reduced the aspartate transaminase (AST) and alanine aminotransferase (ALT) levels to enhance insulin sensitivity of the liver and stabilize blood glucose level in diabetic patients [29]. Furthermore, a continuous human trial conducted by Somanah and co-workers showed that the supplementation of FPP successfully reduced erythrocyte hemolysis rate in pre-diabetics. FPP possessed hydroxyl-quenching properties that could possibly prevent DNA damage and boost the total phenolic content that exhibited antioxidant activities [30].

Unripe papaya has been used as a folk medicine, e.g., to relieve menstrual pain, improve ingestion, wound healing, and heart disease. An in vitro study showed that unripe *Carica papaya* fruit inhibited α-amylase and α-glucosidase enzymes. In addition, the fruit extract protected β-cell against oxidative stress in streptozotocin induced diabetes rats. The phytochemical analysis of *Carica papaya* fruits revealed the presence of phytochemicals, including kaempferol, quercetin, and caffeic acid [31].

An in vivo study suggested that chloroform extract of *Carica papaya* leaves protected β-cells of islet of Langerhans from oxidative stress-induced damage and promoted pancreatic β-cells regeneration at a dose of 31 mg/kg, leading to an increase in insulin production [32]. In addition, Juarez-Rojop and colleagues reported that *Carica papaya* leaf extract stimulated the healthy β-cells to release more insulin in vivo. At concentrations of 0.75 and 1.5 g/100 mL, *Carica papaya* leaf aqueous extract also demonstrated antioxidant properties via increasing NO production, consequently lowering ROS production, and diminishing diabetes-induced oxidative stress. As a result, this mechanism delayed or prevented the progression to diabetic complications, such as neuropathy and nephropathy [33].

3.3. Alzheimer's Disease (AD)

Oxidative stress is correlated with the induction and progression of Alzheimer's disease (AD). AD is manifested by generation of neurofibrillary tangles and an aggregation of β-amyloid peptides in the brain [34]. As the amount of β-amyloid accumulates, it generates ROS that causes lipid and protein peroxidation in the brain, and resultant in neurotoxicity. In an AD brain, there is an impairment of the defense mechanism against oxidative stress due to a reduction in the concentration of glutathione. Furthermore, generation of ROS in the brain inhibits the activity of α-secretase whilst promoting the activity of γ- and β-secretase via generation of neurotoxic β-amyloid 40 and 42 [35]. These two mechanisms form a vicious cycle in the AD pathology. Another mechanism notably suggested that β-amyloid impairs mitochondrial function of neuronal cells in AD patients; therefore, promoting neuronal cell death by inducing oxidative injury in isolated mitochondria. β-amyloid impairs the antioxidative stress mechanism by lowering the expression of uncoupling proteins (UCPs) that act to promote mitochondrial uncoupling and reduce ROS generation [35]. A limited number of studies proposed that oxidative stress susceptibility is increased by overexpression of tau protein in neuronal cells. In addition, presence of transition metals including iron, zinc, and copper can react with the β-amyloid to produce hydrogen peroxide (H_2O_2) in the brain [34–36].

Fermented papaya preparation (FPP) is a popular health-promoting product which owns protective properties against free radicals to improve general health. Meanwhile, fermented papaya preparation (FPP) exerted neuroprotective properties against copper induced neurotoxicity in Swedish mutant human APP (APPsw) cells at a dose of 2.4 mg/mL by reducing 64% of ROS generation. In addition, FPP significantly reduced scavenging of superoxide anion and hydroxyl radicals and upregulation of SOD-1 enzyme. FPP exerted anti-apoptotic effect and attenuated pro-apoptotic Bax gene expression, upregulated BCL level, and maintained calcium homeostasis, leading to improvement of neuronal cell survival and AD condition. Administration of 2.4 mg/mL FPP inhibited up-regulation of expression of iNOS, nNOS, and NO by about 43%, 71%, and 40%. Moreover, treatment with 2.4 mg/mL FPP lowered the secretion of Aβ peptide by 30.6% [37].

FPP significantly reduced the 8-hydroxy2′-deoxyguanosine (8-OHdG) level in AD patients treated with FPP at a dose of 4.5 g/day for 6 months. During the study period, no neurotrophic drugs were administered to the study participants; therefore, proving the value of the *Carica papaya* plant in improving AD. The proposed mechanisms of action by FPP include decreased peroxidation of lipids, aluminum and iron induced neuronal toxicity and free radicals' production [38]. Overall, FPP showed promising anti-Alzheimer's disease in cell-based model and human trial. Studies including discovery of novel phytochemicals, safety profile, and efficacy warrants future investigation.

3.4. Periodontal Disease

Periodontal disease is an infection on the tissue that supports the tooth, which is closely related to oxidative stress. Several examples of periodontal diseases include gingival inflammation, chronic periodontitis, aggressive periodontitis, necrotizing periodontal disease and periodontal associated lesion. These conditions can happen to anyone ranging from a juvenile to an adult [39]. When the integrity of tissues supporting the tooth is compromised, the immune response of the host is triggered secondary to pathogen invasion and eventually led to inflammation. Periodontal inflammation can be augmented by excessive ROS and leukocytes and damaging the periodontal tissues. Likewise, periodontal tissue injury also occurs when there is a disruption in the redox equilibrium, due to either over-generation of ROS or diminished antioxidant enzymes, including GPx, CAT, and SOD, which defend against oxidative stress. ROS plays a role in activating signaling pathways, such as NLRP3 inflammasomes, NF-κB, and JNK, which eventually lead to inflammation and cell death [40]. Human trial has shown that *Carica papaya* leaf extract significantly alleviated gingival bleeding and inflammation [41].

Kharaeva and colleagues reported that the standardized fermented papaya gel (SFPG) application at 7 g/day for 10 consecutive days significantly reduced gingival inflammation and bleeding in participants by decreasing nitrate (NO_3^-) and nitrite level (NO_2^-), and regulating the level of inflammatory cytokines. Reduced NO_3^- and NO_2^- attenuated production of peroxynitrite and oxidative stress generation. Furthermore, the antioxidant effect was reported to last as long as 35 days after stopping SFPG application. Interestingly, SFPG was able to augment bacterial killing by impeding activation of bacterial catalase and eventually prevent infection at the periodontal sites [42].

Studies have also shown the protective effects of *Carica papaya* leaf extract dentifrice on interdental gingival bleeding. Participants who used dentifrice containing *Carica papaya* leaf extract demonstrated a significant decrease in the gingival bleeding and inflammation especially in advanced (>70%) gingival bleeding cases. This result could be attributed to the high phenolic content of *Carica papaya* leaf extract that possess antioxidant properties. A study revealed that *Carica papaya* leaf extract exerted anti-inflammatory action by decreasing TNF-α [41].

3.5. Skin Aging

Skin aging is characterised by extracellular matrix (ECM) degradation in which human skin naturally becomes drier, thinner, unevenly pigmented, and wrinkled, as a human being ages, due to the inevitable intrinsic aging factors. Extrinsic aging factors are avoidable, in which both factors may synergize and lead to premature skin aging. ROS is known to be the culprit of skin aging by contributing to oxidative stress and inflammation. Photoaging is a process that produces ROS, which eventually leads to augmented ECM turnover and degradation. Although not fully deleterious to the cells, excessive ROS can oxidise skin proteins and lipids leading to roughen the skin by altering the function of the skin barrier and further stimulate wrinkle formation [43].

In addition, ultraviolet (UV) and UV-generated ROS hasten aging via activation of mitogen-activated protein kinase (MAPK), p38, Jun N-terminal kinase (JNK), extracellular-signal-regulated kinase (ERK), recruitment of c-Fos, and c-Jun, as well as increased expression of activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB). AP-1 is known to

lower transforming growth factor-beta (TGF-β), which is responsible for collagen production and induce expression of matrix metalloproteinase (MMP) 1, 3, and 9 in keratinocytes, and fibroblast leading to the disruption and loss of ECM components (collagen and elastic fibers) [43]. UV and ROS causes the skin to be in the state of "sunburn" (erythema). This further stimulates production of advanced glycation end products (AGEs). Activation of receptor for AGEs (RAGE) increases NF-κB activation, thereby upregulates pro-inflammatory gene transcriptions and RAGE leading to a vicious inflammatory state cycle characterised by elevated PGE2 synthesis [43,44].

Furthermore, ROS induces melanogenesis by increasing the number of tyrosinase-related protein 1 (TYRP-1) and tyrosinase, which are both known as melanogenic factors resulting in skin pigmentation [44]. In addition, UV radiation induced greater amounts of oxidised lipids, triglyceride hydroperoxides, and cholesterol hydroperoxides generation, leading to increased sebum secretion. This condition in turn promotes the formation of acne vulgaris by *Propionibacterium acnes* (*P. acnes*). *P. acnes* infects skin cells and will further induce the production of free oxygen radicals that eventually lead to the formation of inflammatory lesions [44].

In past decades, research on strategies against skin aging attracted a great attention of researchers. For instance, *Carica papaya* is a potential candidate to be exploited for its anti-skin aging specialty, owing to its antioxidant and anti-inflammatory activities. Table 3 shows anti-skin aging activities of *Carica papaya* extracts. An in vitro study by Jarisarapurin and colleagues focused on unripe *Carica papaya* fruit extract against skin aging related endothelial oxidative stress [45]. It was proposed that activated endothelial cells contributed to a low-grade inflammatory state and the generation of oxidative stress. As a result of this unfavorable microenvironment, MMP-1 expression in dermal fibroblasts was induced leading to a significant loss of type I collagen, and accelerated ECM degradation [46]. The study demonstrated the ability of unripe *Carica papaya* fruit extract to inhibit H_2O_2-induced endothelial cell death at concentrations ranging from 100 to 1000 μg/mL. It was found to exert its effect via modulating intracellular stress and antioxidant defenses in endothelial cells. The mechanisms were consisted of a dose-dependent ROS scavenging effect and NF-κB attenuation, upregulation of SOD and CAT activities, and prevention of H_2O_2-induced Nrf2 over activation. The study further explained that, although activation of antioxidant defenses was prompted by uncoupling of the Nrf2/Keap1 complex, followed by translocation of Nrf2 into the nucleus, the early (or over activation) of Nrf2 induced by oxidative stress can lead to depletion of endogenous antioxidants. The consequence of depletion of natural antioxidants produced by skin cells may promote skin aging. Therefore, the restraining properties of unripe *Carica papaya* on NF-kB elevation and Nrf2 dysregulation were proposed to be beneficial in maintaining redox homeostasis, thereby delaying skin aging [45].

A recent study by Seo and colleagues investigated the anti-aging mechanisms of *Carica papaya* leaf ethanol extract on UVB-irradiated human dermal fibroblast cells in vitro. At concentrations ranging from 10 to 250 μg/mL, the extract demonstrated radical scavenging and ROS suppressing action in a dose-dependent manner. At concentrations of 1 to 50 μg/mL, the extract was shown to enhance synthesis and attenuate degradation of type I procollagen in UVB-irradiated fibroblasts, increment in TGF-β1, and reduction in MMPs (MMP-1 and MMP-3) generation. Interestingly, Seo and colleagues further evaluated that the leaf extract possessed reversal action on UVB-induced AP activation at mRNA level via downregulating MAPK activation and protein phosphorylation of c-Fos and c-Jun. The effect of *Carica papaya* leaf extract on MAPK was proposed to act mainly on p38, showing 82% inhibition against p38 phosphorylation, followed by ERK and JNK. The extract demonstrated to acquire anti-inflammatory action by depleting production of cytokines, such as IL-6. Wrinkles formation induced by sun exposure as a result of erythema and diminished Type I collagen in skin. The ROS-conquering mechanisms and collagen synthesis promoting effects were described by Seo and colleagues, lending support on the potential use of *Carica papaya* leaf extract against skin aging [47].

Table 3. Anti-skin aging of *Carica papaya*.

Part of the Plant	Extract	Type of Experiment	Results	Reference
Unripe papaya juice		In vitro antioxidant enzyme assays	Papaya juice at 1 mg/mL enhanced SOD (49%) and CAT (40.5%) activities.	[45]
		Western blot analysis	Papaya juice at 1 mg/mL restrained NF-κB translocation to nuclei and downregulated Nrf2 levels.	
Leaf	Ethanol extract	In vitro DPPH assay	Ethanol extract at 250 µg/mL showed ROS scavenging effect at 60%.	[47]
		In vitro DCFH-DA assay	Ethanol extract at 50 µg/mL showed potent suppressing action towards UVB-induced ROS production (60%).	
		In vitro MMPs and inflammatory cytokines production	Ethanol extract at 50 µg/mL of *Carica papaya* leaves enhances synthesis and prevents degradation of type I collagen via upregulating TGF-β1 and down-regulating MMP-1 (34% at 50 µg/mL), MMP-3, and IL-6 generation. Ethanol extract at 50 µg/mL of *Carica papaya* leaves reduced mRNA level of MMP-1 (56.8%) and type I procollagen (288.8%).	
		Western blotting assay	Ethanol extract at 50 µg/mL showed AP-1 activation via down-regulating c-Fos (89%) and c-Jun (44%) phosphorylation. Ethanol extract at 50 µg/mL attenuated MAPK activation, and p38 phosphorylation (82%), followed by ERK, and JNK phosphorylation.	
	FPP	Double-blinded RCT	FPP at a dose of 4.5 g showed anti-skin aging by demonstrating overall higher skin moisturization, elasticity, and surface evenness. FPP at a 4.5 g inhibited MDA production and up modulation of AQP-3, enhanced SOD and NO levels in FPP-treated group. FPP at 4.5 g downregulated pro-aging factors (CyPA and CD147 genes) suggesting to reduce risk of skin carcinogenesis.	[48]

Abbreviation: DPPH, 2,2-diphenyl-1-picryl-hydrazyl-hydrate; DCFH-DA, dichloro-dihydro-fluorescein diacetate; SOD, superoxide dismutase; MMP, matrix metalloproteinase; RCT, randomized controlled trial, MDA, serum malondialdehyde.

A human trial by Bertuccelli and colleagues revealed that sublingual FPP 4.5 g sachet twice daily lowered biomarkers of skin aging. While both treatments attenuated skin MDA level, FPP showed superior anti-aging effects than antioxidant cocktails [45]. In addition, FPP elevated levels of SOD, NO, aquaporin-3 (AQP-3), and down-modulation of pro-aging cyclophilin-A (CyPA) and CD147 genes. The study proposed that the regulating effects of FPP on AQP-3 and pro-aging factors were crucial for significant improvement in skin health [48].

The potentiality of *Carica papaya* being formulated as cosmetic products was demonstrated by Saini and colleagues, as the ideal oil-in-water *Carica papaya* fruit cream prepared was uniform, stable, and had a shiny and smooth texture. This study further proved ROS suppression as the main mechanism of *Carica papaya* fruit against anti-aging, in which the 5% cream was potent, owing reducing power against H_2O_2 free radicals [49].

Flavonoids and phenolic acids were found in *Carica papaya* leaf and fruit extracts [50,51]. Flavonoids in *Carica papaya* are mainly kaempferol, myricetin, quercetin, and their glycosides, phenolic acids, such as caffeic acid and ferulic acid, are the key ROS suppressors

and antioxidant that displayed radical scavenging and metal chelating potential [50,52]. Caffeic acid and rutin were detected and proposed to be the main anti-skin aging components. Both phytochemicals were reported to downregulate MMPs expression and photoprotective against collagen degradation. Caffeic acid mitigated skin erythema via inhibitory action towards NF-κB and AP-1 signaling [48]. The ability of caffeic acid in film formulation to permeate and retentate in epidermis (stratum corneum) and dermis layer enhance its efficacy [50,53]. Besides, the anti-skin aging role of rutin was supported by a human trial, which showed enhanced skin elasticity and less wrinkles in individuals treated with rutin-containing cream. The findings of elevated type I collagen via lowering MMP expression and potent ROS scavenging in human dermal fibroblast cells further supported the anti-skin aging of *Carica papaya* chemical constituents [48,54].

Albeit several mechanisms were compiled and proposed, however, studies regarding the *Carica papaya* anti-skin aging effect were scarce. More evidence regarding various parts, therapeutic range, and the relevant phytochemicals of *Carica papaya* on skin aging are needed to ensure their efficacy.

3.6. Wound Healing

Wound healing is rather complex and well-coordinated with involvement of several stages of cellular responses, including inflammation, proliferation, and remodeling. The duration of each phase usually ranges from 1 to 4 days, 5 to 10 days, and 11 days onwards. Characterisation for each phase includes presence of leukocytes, angiogenesis, protein synthesis and deposition, epithelialization, wound contraction, and scar formation [55]. These processes can be altered by the presence of oxidative stress [56]. The efficiency of the wound healing process decreases with advancing age [57]. Oxidative stress can alter the speed of wound recovery as it depends on the amount of ROS present at the wound site. Although minimal ROS prevents infection, excessive ROS is known cytotoxic to fibroblasts and reduce flexibility of skin lipids. In addition, it also causes impairment to lipids, DNA, proteins, and cellular membranes, and subsequently, severely damages the tissue and promotes inflammation [56].

In the case of chronic wounds or impaired wounds, ROS production is excessive in response to NADPH oxidase (NOX) activation in macrophages and neutrophils during the inflammatory phase of the wound healing process, contributing to high oxidative stress that leads to the wound remaining not healed. Thereby, extracts and phytochemicals with great strength of antioxidative properties are beneficial in wound healing [58,59]. Another key factor for wound healing is the extent of inflammation level at different stages of healing. Inflammation is essential to prevent infection, stimulate angiogenesis, and matrix deposition via secretion of cytokines and angiogenic factors at the early stage of wound healing. However, excessive or prolonged pathological inflammation causes delayed wound healing and fibrosis. Hence, inflammation at certain phases is deemed crucial for wound healing, but not throughout the entire healing process [55,60].

It is known that oxidative stress plays a vital role in wound healing. Table 4 shows wound healing activities of *Carica papaya* extracts. The protective action of aqueous extract *Carica papaya* seeds against oxidative stress-induced apoptosis in human skin fibroblast further supported its role in wound healing. An extensive mechanistic study conducted found potent antioxidant action of the papaya extract against H_2O_2-induced oxidative stress specifically on fibroblast cells was activated via radical scavenging, reduction of calcium ions influx into cytoplasm, reversal of oxidative stress-induced mitochondrial dysfunction, and maintaining oxidative balance inside the cells [61]. Mikhal and colleagues showed that FPP possesses antioxidative stress and anti-inflammation activities. FPP inhibited superoxide (IC_{50} = 5 mg/mL), hydroxyl radicals (IC_{50} = 1.1 mg/mL), and total ROS (IC_{50} =2 mg/mL) in blood, as well as reduction in myeloperoxidase (MPO) and radical generation at wound sites in vivo [62].

In addition, topical application of 5 mg/mL *Carica papaya* fruit extract enhanced wound healing by exerting effect on regulation antioxidant enzymes, inflammation, and

arginine metabolism. The addition of an antioxidant, selenium to the regimen, further shortened the time for wound healing significantly and, hence, confirmed the mechanisms. Antioxidative stress related mechanisms include inhibition of lipid peroxidation, lower MDA level and enhanced expression of SOD, CAT, and GPx. *Carica papaya* fruit extract reduces inflammation associated with oxidative damage through upregulation of antioxidant enzymes, arginine metabolism, and cyclooxygenase specific inhibition in an excision wound model. The extract demonstrated an attenuated inflammatory state, increased collagen synthesis and vascularization at wound site. Transforming growth factor-beta (TGF-β), a cytokine that generates fibroblast recruitment was high at the inflammatory phase and reduced at the repairing phase. While expression of vascular endothelial growth factor A (VEGFA), an angiogenic factor was increased throughout the wound healing process. The further study showed that addition of selenium to the papaya fruit extract synergistically upregulated TGF-β and VEGFA resulting in a significant acceleration in the wound healing process [63,64].

An oral FPP supplementation at a dose of 0.2 g/kg body weight for 8 weeks was found to enhance diabetic wound closure via improved macrophages respiratory-burst function and iNOS production. Diabetic wounds are hard-to-heal due to being prone to infections as a result of compromised NO at the wound site. Another reason was the antibacterial effect of macrophages via NOX was downregulated by hyperglycemia, consequently, respiratory burst dysfunction was seen in diabetic patients. FPP was shown to reverse these conditions. Similar to previous report by Nafiu and colleagues, FPP supplement showed an increase in VEGFA expression, deemed as a crucial regulator in current scenario [65].

Dickerson and colleagues further examined the diabetic wound healing effect of FPP on type II diabetes mellitus patients. The participants were given oral FPP (9 g/day for 6 weeks), and showed that NADPH and cellular ATP level increased in human monocytic THP-1 cells treated with FPP. Besides, FPP also exhibited higher oxygen usage and mitochondrial membrane potential on monocytic cells, which further revealed its capability to correct the respiratory burst function, enhancing the defense mechanisms against pathogens in diabetics. FPP upregulated the mRNA expression of Rac2, which was essential for NOX activation and eventually enhancing respiratory burst in macrophages [66,67].

Meanwhile, Indran and colleagues investigated the protective effect of *Carica papaya* leaf aqueous extract against alcohol-induced hemorrhagic lesions. Pretreatment with 500 mg/kg leaf extract significantly reduced gastric ulcer index via reducing lipid peroxidation, MDA levels, and improving GPx activity at gastric mucosa. The study showed the radical scavenging activity, which might be contributed by polyphenols within leaf extract. It was suggesting that the alkaline content of the extract and its ability to neutralize stomach acidity, thereby protecting stomach against gastric ulcer [68]. The concepts were further supported by in vivo studies evaluating different parts of *Carica papaya* on incised, burned, and diabetic wounds respectively. The recent findings show that *Carica papaya* fruit and seed extracts demonstrated dose-dependent increment in hydroxyproline, fibrillation, epithelial thickness, shortened wound contraction, and epithelialization time [69–72].

Cysteine endopeptidases including papain and chymopapain showed wound healing activity that can be attributed to their proteolytic wound debridement and antibacterial effects [63,64,70,72]. This was established by an in vivo study using papain-based wound cleanser. The cleanser was formulated with 5 g of papain and α-tocopherol. The results showed superior collagen deposition and least fluid exudates compared to betadine cleanser leading to eschar reduction and quicker epithelialization [73]. Safety of *Carica papaya* extracts and dressings is of less concern as it is traditionally used to treat wounds and certain skin conditions [74]. Several studies further assured its safety to be used [61,67,71]. In addition, papaya dressing was safe to be used and compatible in hydrogel formulation [70,75].

Table 4. Wound healing activities of *Carica papaya*.

Part of the Plant	Extract	Type of Experiment	Results	Reference
Seed	Aqueous extract	In vitro cytoprotective assay	Aqueous extract of papaya seeds at 1mg/mL showed cytoprotective against H_2O_2 induced cell toxicity.	[61]
		Cell apoptosis assay	Aqueous extract of papaya seeds at a concentration of 1 mg/mL inhibited H_2O_2 induced apoptosis by approximately 30%.	
		MMP and Cytochrome C assay	Seed extract at 1 mg/mL inhibited oxidative stress-induced cell apoptosis, reduced mitochondrial dysfunction and impeded release of cytochrome C.	
		Western blot analysis	1 mg/mL of seed extract decreased overexpression of HSP-70 in fibroblasts.	
-	Fermented papaya (Biorex)	In vitro HRBC model	Biorex inhibited superoxide (IC_{50} = 5 mg/mL), hydroxyl radicals (IC_{50} = 1.1 mg/mL), and total ROS (IC_{50} = 2 mg/mL) in human red blood cells.	[62]
		In vitro animal model	Biorex (1–5 mg/mL) decreased the elevated radical generation in rats with burn trauma. Biorex reduced local inflammation and catalase activity.	
Unripe pulp	Papaya extract +/− Selenium	In vitro animal model	Papaya extract alone (PE) or with selenium (PES) enhanced wound closure in rats. Both PE and PES augmented SOD, CAT, and GPx activities. PE with selenium ameliorated oxidative damage at the wound site. PE enhanced wound healing via attenuating excessive inflammation, reduced COX-2, and MPO enzyme activity. PE and PES increased NO content by increasing iNOS, stimulating collagen deposition and angiogenesis. PE suppressed arginase activity during wound healing as indicated by decreased wound urea content.	[63]
Unripe papaya pulp	Papaya aqueous extract. Or Papaya PBS extract + Selenium	In vitro animal model	Total protein content (95.14 ± 1.15 mg/g tissue) in wound tissue was significantly higher in rats treated with PES at a dose 5 mg/mL twice daily for papaya and 0.5 µg/20 mL for selenium. Rats treated with PES demonstrated elevation in wound hydroxyproline (*55.15 ± 1.06 µg/mg), hexuronic acid (*60.84 ± 6.08 mg/g), and hexosamine (*35.23 ± 4.95 mg/g) contents. Overall reduced in migration of polymorphonuclear monocytes and increased fibroblast recruitment at wound sites. PE enhanced collagen synthesis and vascularization. Time required for wound closure was shortened, indicated by earlier increment in VEGFA and TGF-β1 expression.	[64]

Table 4. *Cont.*

Part of the Plant	Extract	Type of Experiment	Results	Reference
-	FPP	In vitro animal model	FPP at a dose of 200 mg/kg s improved wound closure via increasing ROS (superoxides) production by macrophages at wound site and promoting NO production at ~60%. Increased NO and ROS to support redox signaling and angiogenesis. FPP increased CD68, VEGF transcription, macrophages recruitment to wound site and promoted optimal angiogenesis environment.	[65]
Leaf	Aqueous extract	In vitro animal model	Aqueous extract of papaya leaves at a dose of 500 mg/kg protected the stomach from absolute ethanol induced injury. Aqueous extract decreased MDA levels by 0.031 µmol/L and increased GPx by 0.246 U/mg protein.	[68]
Fruit	Aqueous extract	In vitro animal model	Aqueous extract of papaya fruit significantly shrank the wound area at 100 mg/kg by 77% by increasing epithelialization rate, weight of dry and wet granulation tissues and promoting enzymatic debridement of wound. Aqueous extract-treated wound showed rapid collagen turnover and accumulation that enhanced wound healing.	[69]
Tree	Dried latex incorporated into hydrogel	In vitro animal model	Topical application of the dried latex-containing hydrogel (1–2.5%) increased hydroxyproline content. Significant wound contraction after application of this hydrogel day 12 at concentration of 2.5% and on day 20 at both concentrations of 1.0% and 2.5%.	[70]
Seed	Ethanol extract	In vitro animal model	Ethanol extract of papaya seeds at a dose of 50 mg/kg significantly reduced wound area by 88.96%. Ethanol extract produces well-organized collagen deposition and significant fibroblast activity.	[71]

Abbreviation: MMP, matrix metalloproteinase; HRBC, human red blood cell; HSP-70, heat shock protein 70; NO, nitric oxide; ROS, reactive oxygen species; COX-2, cyclooxygenase-2; MPO, myeloperoxidase; VEGFA, vascular endothelial growth factor A; TGF, transforming growth factor; FPP, fermented papaya preparation; MDA, serum malondialdehyde.

3.7. Cancers

Cancer is a prevailing topic and there is no absolute cure to date for various types of cancers. ROS generation as a result of metabolic reactions in the mitochondria plays a role in both initiation and potentially elimination of cancers. With a low amount of ROS that is tolerable by the body cells, the progression of cancer could occur through either promoting genomic DNA alterations or DNA damage that alters the normal physiological signaling pathways. For instance, mitogen-activated protein kinase (MAPK) activation, c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK) phosphorylation, and cyclin D1 expression are correlated to cancer progression and survival [76]. In the normal healthy cells, a significantly high level of ROS can lead to cellular damage and eventually cell death [77]. However, cancer cells generally have a higher resistance to oxidative stress than normal cells to allow for uncontrolled proliferation and to compensate for the survival

of cancer cells during metastasis from their site of origin [76]. However, increasing ROS to a specific threshold level, specifically for cancer cells is proven to attenuate cancer cell growth and progression.

Several studies showed the correlation of microRNAs and oxidative stress in the progression of cancer. The recent advancement of genomic studies has showcased the presence of certain groups of microRNAs may promote cancer cell proliferation and progression. For example, there is an overexpression of miR-210 detected in hepatocellular and breast carcinoma under hypoxia. miR-210 acts to regulate the ROS production and mitochondrial function by promoting cancer cell adaptation, survival, and proliferation [77]. It also suggested that ROS is able to induce carcinogenesis by induced mutations in the tumour-suppressor gene in the normal skin cells leading to a transformation of normal cell into cancerous cells by halting the initiation of programmed cell death. An example of this mutation is seen in the alteration of a guanine in the p53 gene through oxidative mechanisms in basal cell and squamous cell carcinoma [43].

DNA damage is pivotal in cancer formation. A study proposed that FPP was capable of impeding DNA fragmentation induced by free radicals and H_2O_2-induced DNA damage at a dose of 100 µg/mL [16]. In addition, the aqueous extract of *Carica papaya* fruit suppressed proliferation of human breast epithelial cancer (MCF-7) cells in vitro. The aqueous extract of *Carica papaya* showed significant anti-proliferation activity (~53%) in MCF-7 cells at a dose of 4% *v*/*v* after 72 h treatment. The anti-cancer activity of FPP might be attributed to the mechanisms including triggering cell signaling to induce apoptosis [78]. An in vitro study showed that the aqueous extract of *Carica papaya* leaves showed antiproliferation activity of MCF-7 at a IC_{50} of 1.31 mg/mL and induced apoptosis of MCF-7 cells at 22.5% with a dose of 0.65 mg/mL [79].

Carica papaya enriched with phytochemicals, including flavonoids, has been found to possess chemopreventive properties. The mechanisms of action underlying the chemoprevention effects include activating tumour-suppressor genes, deactivating oncogene products transcriptionally, decreasing oxidative damage via acting as free radical scavengers and impeding the commencement of lipoxygenase reaction by chelating with ROS-generating agents. For example, the benzene fraction of aqueous extract of *Carica papaya* showed chemoprotective effects in benzo(a)pyrene and 7,12-dimethyl benz(a)anthracene -induced carcinogenic animal models. It was reported that a significant reduction of lung adenomas (>50%) at a treatment dose of 1 g/kg body weight. In addition, a significant reduction in skin papillomagenesis incidence at 64.20% was compared with tumour incidence in the control group. It was suggested that those flavonoids contained within different parts of the *Carica papaya* plant act via multi-signaling networks as the viable chemoprevention agents [80].

An in vivo study reported that FPP at a concentration of 500 mg/kg significantly elevated antioxidant enzymes, including GPx (66.1%), SOD (20%), and CAT (81%). Furthermore, FPP was also capable of preventing DNA structural damage possibly induced by free radicals and genotoxins [81]. This was supported by another study suggesting that *Carica papaya* peel extract significantly increased glutathione (GSH), while decreasing MDA and ROS production. Thus, preventing DNA damage and induction of colonic carcinogenesis azoxymethane treated group [82]. Another study by Mukami and colleagues revealed that orally administration of FPP at 450 mg/kg showed complete disappearance of the tumours in a radiation-induced leukemia mice model [83]. Overall, several research groups revealed the anticancer properties of papaya extracts. Further studies are needed to standardize the extract for quality control of the efficacy, and discover novel compounds, owing to the anticancer activities.

4. Conclusions

To summarize, the *Carica papaya* counteracts oxidative stress via its potent antioxidant properties. Therefore, it can be incorporated into nutraceuticals or conventional medications to be used as a potential preventative or treatment option for various health

conditions. The antioxidant properties of the *Carica papaya* plant might be attributed to the various chemical constituents that the plant contains, including caffeic acid, myricetin, quercetin, rutin, α-tocopherol, papain, BiTC, kaempferol steroids, alkaloids, and saponins.

There is no doubt that emerging evidence has proven the potential of *Carica papaya* as a natural resource that can be exploited as a medicinal product. However, more safety data are needed to justify its use in different medical conditions. Many plants—although exerting therapeutic benefits, having been used traditionally for diseases since the ancient times—are potentially cytotoxic [7,84]. The acute toxicity study of the *Carica papaya* leaf extract revealed that there were no significant toxic effects of *Carica papaya* leaf extract at the concentration up to 2 g/kg of body weight, which corresponded to 14 times the dose incorporated in traditional medication. Moreover, it was also suggested that any concentration of *Carica papaya* leaf extract below 2 g/kg of body weight posed no significant toxicity and adverse effects when administered orally for a 14-day interval [85,86]. In terms of the *Carica papaya* extract with different methods of extraction, namely ethanol and aqueous extract, it might possess different safety profiles, owing to the extractive chemical constituents. For example, the ethanol extract might be more nephrotoxic and hepatotoxic than the aqueous extract in the Wistar rats model at 1 g/kg of body weight concentration [87]. However, all these studies suggest that more extensive evaluation studies pertaining the cytotoxicity profile of oral administration of the *Carica papaya* extract are needed to further validate the safety for consumption.

It was also suggested that the medicinal properties of the *Carica papaya* plant can be attributed to other mechanisms of action. Several studies have suggested that *Carica papaya* extract exerted antimicrobial properties that aided in wound recovery [69,71]. Therefore, more studies should be done in order to unravel the benefits of the *Carica papaya*.

Author Contributions: Conceptualization, K.Y.K. Writing–original draft preparation, Y.R.K., Y.X.J., M.B., Z.K.B., J.K.K.W. and K.C.T. Writing—review and editing, Y.R.K., Y.X.J., M.B., Z.K.B., J.K.K.W., K.C.T., K.G.C., L.H.L., B.H.G., K.Y.K. and Y.S.O.; supervision, K.Y.K. and Y.S.O. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the University of Malaya (to Kok-Gan Chan, FRGS grant number: FP022-2018A) and The SEED Funding from Microbiome and Bioresource Research Strength (MBRS), Jeffrey Cheah School of Medicine and Health Sciences, (To Learn-Han Lee, Vote Number: MBRS/JCSMHS/02/2020).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to acknowledge School of Pharmacy, Monash University Malaysia for administrative and technical support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sies, H. Oxidative stress: A concept in redox biology and medicine. *Redox Biol.* **2015**, *4*, 180–183. [CrossRef]
2. Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 8416763. [CrossRef] [PubMed]
3. Aradhya, M.K.; Manshardt, R.M.; Zee, F.; Morden, C.W. A phylogenetic analysis of the genus Carica, L. (Caricaceae) based on restriction fragment length variation in a cpDNA intergenic spacer region. *Genet. Resour. Crop Evol.* **1999**, *46*, 579–586. [CrossRef]
4. Yogiraj, V.; Goyal, P.; Chauhan, C.S.; Goyal, A.; Vyas, B. *Carica papaya* Linn: An overview. *Int. J. Herb. Med.* **2014**, *2*, 1–8.
5. Yap, J.Y.; Hii, C.L.; Ong, S.P.; Lim, K.H.; Abas, F.; Pin, K.Y. Effects of drying on total polyphenols content and antioxidant properties of *Carica papaya* leaves. *J. Sci. Food Agric.* **2020**, *100*, 2932–2937. [CrossRef]
6. Fei, X.; Yuan, W.; Zhao, Y.; Wang, H.; Bai, S.; Huang, Q. Papain Ameliorates the MPAs Formation-Mediated Activation of Monocytes by Inhibiting Cox-2 Expression via Regulating the MAPKs and PI3K/Akt Signal Pathway. *BioMed Res. Int.* **2018**, *2018*, 3632084. [CrossRef]

7. Silva, C.R.d.; Oliveira, M.B.N.; Motta, E.S.; Almeida, G.S.d.; Varanda, L.L.; Pádula, M.d.; Leitão, A.C.; Caldeira-de-Araújo, A. Genotoxic and Cytotoxic Safety Evaluation of Papain (*Carica papaya* L.) Using In Vitro Assays. *J. Biomed. Biotechnol.* **2010**, *2010*, 197898. [CrossRef]
8. Park, M.J.; Bae, Y.S. Fermented Acanthopanax koreanum Root Extract Reduces UVB- and H2O2-Induced Senescence in Human Skin Fibroblast Cells. *J. Microbiol. Biotechnol.* **2016**, *26*, 1224–1233. [CrossRef]
9. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget* **2017**, *9*, 7204–7218. [CrossRef] [PubMed]
10. Luster, A.D. The role of chemokines in linking innate and adaptive immunity. *Curr. Opin. Immunol.* **2002**, *14*, 129–135. [CrossRef]
11. Morgan, M.J.; Liu, Z.-g. Crosstalk of reactive oxygen species and NF-κB signaling. *Cell Res.* **2011**, *21*, 103–115. [CrossRef]
12. Hussain, T.; Tan, B.; Yin, Y.; Blachier, F.; Tossou, M.C.B.; Rahu, N. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? *Oxidative Med. Cell. Longev.* **2016**, *2016*, 7432797. [CrossRef] [PubMed]
13. Kanda, Y.; Osaki, M.; Okada, F. Chemopreventive Strategies for Inflammation-Related Carcinogenesis: Current Status and Future Direction. *Int. J. Mol. Sci.* **2017**, *18*, 867. [CrossRef]
14. Chatterjee, S. Chapter Two—Oxidative Stress, Inflammation, and Disease. In *Oxidative Stress and Biomaterials*; Dziubla, T., Butterfield, D.A., Eds.; Academic Press: Cambridge, MA, USA, 2016; pp. 35–58. [CrossRef]
15. Wijesooriya, A.; Deraniyagala, S.; Hettiarachchi, C. Antioxidant, Anti-Inflammatory and Antibacterial Activities of the Seeds of A Sri Lankan Variety of *Carica papaya*. *Biomed. Pharmacol. J.* **2019**, *12*, 539–547. [CrossRef]
16. Aruoma, O.I.; Colognato, R.; Fontana, I.; Gartlon, J.; Migliore, L.; Koike, K.; Coecke, S.; Lamy, E.; Mersch-Sundermann, V.; Laurenza, I.; et al. Molecular effects of fermented papaya preparation on oxidative damage, MAP Kinase activation and modulation of the benzo[a]pyrene mediated genotoxicity. *Biofactors* **2006**, *26*, 147–159. [CrossRef] [PubMed]
17. Zuhrotun Nisa, F.; Astuti, M.; Mubarika Haryana, S.; Murdiati, A. Effect of Papaya Leaves (*Carica papaya* L.) Extract on Immune Response (TLR-7, TLR-9) and Inflammation (COX-2) in Rats Induces DMBA (7,12-Dimethylbenz[a]antrasen). *Pak. J. Biol. Sci.* **2020**, *23*, 1450–1455. [CrossRef] [PubMed]
18. Somanah, J.; Bourdon, E.; Bahorun, T. Extracts of Mauritian *Carica papaya* (var. solo) protect SW872 and HepG2 cells against hydrogen peroxide induced oxidative stress. *J. Food Sci. Technol.* **2017**, *54*, 1917–1927. [CrossRef] [PubMed]
19. Od-Ek, P.; Deenin, W.; Malakul, W.; Phoungpetchara, I.; Tunsophon, S. Anti-obesity effect of *Carica papaya* in high-fat diet fed rats. *Biomed. Rep.* **2020**, *13*, 30. [CrossRef]
20. Owoyele, B.V.; Adebukola, O.M.; Funmilayo, A.A.; Soladoye, A.O. Anti-inflammatory activities of ethanolic extract of *Carica papaya* leaves. *Inflammopharmacology* **2008**, *16*, 168–173. [CrossRef] [PubMed]
21. Amazu, L.U.; Azikiwe, C.C.A.; Njoku, C.J.; Osuala, F.N.; Nwosu, P.J.C.; Ajugwo, A.O.; Enye, J.C. Antiinflammatory activity of the methanolic extract of the seeds of *Carica papaya* in experimental animals. *Asian Pac. J. Trop. Med.* **2010**, *3*, 884–886. [CrossRef]
22. Ahmed, M.; Ramabhimalah, S. Anti-Inflammatory Activity of Aqueous Extract of *Carica papaya* Seeds in Albino Rats. *Biomed. Pharmacol. J.* **2012**, *5*, 173–177. [CrossRef]
23. Skyler, J.S.; Bakris, G.L.; Bonifacio, E.; Darsow, T.; Eckel, R.H.; Groop, L.; Groop, P.-H.; Handelsman, Y.; Insel, R.A.; Mathieu, C.; et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. *Diabetes* **2017**, *66*, 241–255. [CrossRef]
24. Maritim, A.C.; Sanders, R.A.; Watkins Iii, J.B. Diabetes, oxidative stress, and antioxidants: A review. *J. Biochem. Mol. Toxicol.* **2003**, *17*, 24–38. [CrossRef] [PubMed]
25. King, G.L.; Loeken, M.R. Hyperglycemia-induced oxidative stress in diabetic complications. *Histochem. Cell Biol.* **2004**, *122*, 333–338. [CrossRef] [PubMed]
26. Rolo, A.P.; Palmeira, C.M. Diabetes and mitochondrial function: Role of hyperglycemia and oxidative stress. *Toxicol. Appl. Pharmacol.* **2006**, *212*, 167–178. [CrossRef]
27. Agada, R.; Usman, W.A.; Shehu, S.; Thagariki, D. In vitro and in vivo inhibitory effects of *Carica papaya* seed on α-amylase and α-glucosidase enzymes. *Heliyon* **2020**, *6*, e03618. [CrossRef] [PubMed]
28. Raffaelli, F.; Nanetti, L.; Montecchiani, G.; Borroni, F.; Salvolini, E.; Faloia, E.; Ferretti, G.; Mazzanti, L.; Vignini, A. In vitro effects of fermented papaya (*Carica papaya*, L.) on platelets obtained from patients with type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* **2015**, *25*, 224–229. [CrossRef]
29. Somanah, J.; Aruoma, O.I.; Gunness, T.K.; Kowelssur, S.; Dambala, V.; Murad, F.; Googoolye, K.; Daus, D.; Indelicato, J.; Bourdon, E.; et al. Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. *Prev. Med.* **2012**, *54*, S90–S97. [CrossRef]
30. Somanah, J.; Bourdon, E.; Rondeau, P.; Bahorun, T.; Aruoma, O.I. Relationship between fermented papaya preparation supplementation, erythrocyte integrity and antioxidant status in pre-diabetics. *Food Chem. Toxicol.* **2014**, *65*, 12–17. [CrossRef]
31. Miranda-Osorio, P.H.; Castell-Rodríguez, A.E.; Vargas-Mancilla, J.; Tovilla-Zárate, C.A.; Ble-Castillo, J.L.; Aguilar-Domínguez, D.E.; Juárez-Rojop, I.E.; Díaz-Zagoya, J.C. Protective Action of *Carica papaya* on β-Cells in Streptozotocin-Induced Diabetic Rats. *Int. J. Environ. Res. Public Health* **2016**, *13*, 446. [CrossRef]
32. Juárez-Rojop, I.E.; Díaz-Zagoya, J.C.; Ble-Castillo, J.L.; Miranda-Osorio, P.H.; Castell-Rodríguez, A.E.; Tovilla-Zárate, C.A.; Rodríguez-Hernández, A.; Aguilar-Mariscal, H.; Ramón-Frías, T.; Bermúdez-Ocaña, D.Y. Hypoglycemic effect of *Carica papaya* leaves in streptozotocin-induced diabetic rats. *BMC Complement. Altern. Med.* **2012**, *12*, 236. [CrossRef] [PubMed]

33. Oboh, G.; Olabiyi, A.A.; Akinyemi, A.J.; Ademiluyi, A.O. Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside-induced lipid peroxidation in rat pancreas by water-extractable phytochemicals from unripe pawpaw fruit (*Carica papaya*). *J. Basic Clin. Physiol. Pharmacol.* **2014**, *25*, 21–34. [CrossRef]
34. Gella, A.; Durany, N. Oxidative stress in Alzheimer disease. *Cell Adh. Migr.* **2009**, *3*, 88–93. [CrossRef] [PubMed]
35. Zhao, Y.; Zhao, B. Oxidative stress and the pathogenesis of Alzheimer's disease. *Oxid. Med. Cell Longev.* **2013**, *2013*, 316523. [CrossRef] [PubMed]
36. Huang, W.-J.; Zhang, X.; Chen, W.-W. Role of oxidative stress in Alzheimer's disease. *Biomed. Rep.* **2016**, *4*, 519–522. [CrossRef]
37. Zhang, J.; Mori, A.; Chen, Q.; Zhao, B. Fermented papaya preparation attenuates beta-amyloid precursor protein: Beta-amyloid-mediated copper neurotoxicity in beta-amyloid precursor protein and beta-amyloid precursor protein Swedish mutation overexpressing SH-SY5Y cells. *Neuroscience* **2006**, *143*, 63–72. [CrossRef]
38. Barbagallo, M.; Marotta, F.; Dominguez, L.J. Oxidative stress in patients with Alzheimer's disease: Effect of extracts of fermented papaya powder. *Mediat. Inflamm.* **2015**, *2015*, 624801. [CrossRef]
39. Highfield, J. Diagnosis and classification of periodontal disease. *Aust. Dent. J.* **2009**, *54* (Suppl. S1), S11–S26. [CrossRef]
40. Liu, C.; Mo, L.; Niu, Y.; Li, X.; Zhou, X.; Xu, X. The Role of Reactive Oxygen Species and Autophagy in Periodontitis and Their Potential Linkage. *Front. Physiol.* **2017**, *8*, 439. [CrossRef]
41. Saliasi, I.; Llodra, J.C.; Bravo, M.; Tramini, P.; Dussart, C.; Viennot, S.; Carrouel, F. Effect of a Toothpaste/Mouthwash Containing *Carica papaya* Leaf Extract on Interdental Gingival Bleeding: A Randomized Controlled Trial. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2660. [CrossRef]
42. Kharaeva, Z.F.; Zhanimova, L.R.; Mustafaev, M.; De Luca, C.; Mayer, W.; Chung Sheun Thai, J.; Tiew Siok Tuan, R.; Korkina, L.G. Effects of Standardised Fermented Papaya Gel on Clinical Symptoms, Inflammatory Cytokines, and Nitric Oxide Metabolites in Patients with Chronic Periodontitis: An Open Randomised Clinical Study. *Mediat. Inflamm.* **2016**, *2016*, 9379840. [CrossRef]
43. Rinnerthaler, M.; Bischof, J.; Streubel, M.K.; Trost, A.; Richter, K. Oxidative stress in aging human skin. *Biomolecules* **2015**, *5*, 545–589. [CrossRef]
44. Masaki, H. Role of antioxidants in the skin: Anti-aging effects. *J. Dermatol. Sci.* **2010**, *58*, 85–90. [CrossRef]
45. Jarisarapurin, W.; Sanrattana, W.; Chularojmontri, L.; Kunchana, K.; Wattanapitayakul, S. Antioxidant Properties of Unripe *Carica papaya* Fruit Extract and Its Protective Effects against Endothelial Oxidative Stress. *Evid. Based Complement. Altern. Med.* **2019**, *2019*, 4912631. [CrossRef]
46. Sanchez, B.; Li, L.; Dulong, J.; Aimond, G.; Lamartine, J.; Liu, G.; Sigaudo-Roussel, D. Impact of Human Dermal Microvascular Endothelial Cells on Primary Dermal Fibroblasts in Response to Inflammatory Stress. *Front. Cell Dev. Biol.* **2019**, *7*, 44. [CrossRef]
47. Seo, S.A.; Ngo, H.T.T.; Hwang, E.; Park, B.; Yi, T.-H. Protective effects of *Carica papaya* leaf against skin photodamage by blocking production of matrix metalloproteinases and collagen degradation in UVB-irradiated normal human dermal fibroblasts. *S. Afr. J. Bot.* **2020**, *131*, 398–405. [CrossRef]
48. Bertuccelli, G.; Zerbinati, N.; Marcellino, M.; Nanda Kumar, N.S.; He, F.; Tsepakolenko, V.; Cervi, J.; Lorenzetti, A.; Marotta, F. Effect of a quality-controlled fermented nutraceutical on skin aging markers: An antioxidant-control, double-blind study. *Exp. Ther. Med.* **2016**, *11*, 909–916. [CrossRef] [PubMed]
49. Saini, R.; Mittal, A.; Rathi, V. Formulation & in vitro antioxidant analysis of anti-ageing cream of *Carica papaya* fruit extract. *IJOD* **2016**, *4*, 8–14.
50. Magnani, C.; Isaac, V.; Corrêa, M.; Salgado, H. Caffeic acid: A review of its potential use in medications and cosmetics. *Anal. Methods* **2014**, *6*, 3203. [CrossRef]
51. Gomes, W.F.; França, F.R.M.; Denadai, M.; Andrade, J.K.S.; da Silva Oliveira, E.M.; de Brito, E.S.; Rodrigues, S.; Narain, N. Effect of freeze- and spray-drying on physico-chemical characteristics, phenolic compounds and antioxidant activity of papaya pulp. *J. Food Sci. Technol.* **2018**, *55*, 2095–2102. [CrossRef] [PubMed]
52. Nugroho, A.; Heryani, H.; Choi, J.S.; Park, H.-J. Identification and quantification of flavonoids in Carica papaya leaf and peroxynitrite-scavenging activity. *Asian Pac. J. Trop. Biomed.* **2017**, *7*, 208–213. [CrossRef]
53. Spagnol, C.M.; Di Filippo, L.D.; Isaac, V.L.B.; Correa, M.A.; Salgado, H.R.N. Caffeic Acid in Dermatological Formulations: In Vitro Release Profile and Skin Absorption. *Comb. Chem. High Throughput Screen.* **2017**, *20*, 675–681. [CrossRef] [PubMed]
54. Choi, S.J.; Lee, S.N.; Kim, K.; Joo da, H.; Shin, S.; Lee, J.; Lee, H.K.; Kim, J.; Kwon, S.B.; Kim, M.J.; et al. Biological effects of rutin on skin aging. *Int. J. Mol. Med.* **2016**, *38*, 357–363. [CrossRef] [PubMed]
55. Midwood, K.S.; Williams, L.V.; Schwarzbauer, J.E. Tissue repair and the dynamics of the extracellular matrix. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1031–1037. [CrossRef]
56. Gonzalez, A.C.; Costa, T.F.; Andrade, Z.A.; Medrado, A.R. Wound healing—A literature review. *Bras. Dermatol.* **2016**, *91*, 614–620. [CrossRef] [PubMed]
57. Lephart, E.D. Skin aging and oxidative stress: Equol's anti-aging effects via biochemical and molecular mechanisms. *Ageing Res. Rev.* **2016**, *31*, 36–54. [CrossRef]
58. Süntar, I.; Akkol, E.K.; Nahar, L.; Sarker, S.D. Wound healing and antioxidant properties: Do they coexist in plants? *Free Radic. Antioxid.* **2012**, *2*, 1–7. [CrossRef]
59. Cano Sanchez, M.; Lancel, S.; Boulanger, E.; Neviere, R. Targeting Oxidative Stress and Mitochondrial Dysfunction in the Treatment of Impaired Wound Healing: A Systematic Review. *Antioxidants* **2018**, *7*, 98. [CrossRef]
60. Singh, S.; Young, A.; McNaught, C.-E. The physiology of wound healing. *Surg. Oxf. Int. Ed.* **2017**, *35*, 473–477. [CrossRef]

61. Panzarini, E.; Dwikat, M.; Mariano, S.; Vergallo, C.; Dini, L. Administration Dependent Antioxidant Effect of *Carica papaya* Seeds Water Extract. *Evid. Based Complement. Alternat. Med.* **2014**, *2014*, 281508. [CrossRef]
62. Mikhal'chik, E.V.; Ivanova, A.V.; Anurov, M.V.; Titkova, S.M.; Pen'kov, L.Y.; Kharaeva, Z.F.; Korkina, L.G. Wound-healing effect of papaya-based preparation in experimental thermal trauma. *Bull. Exp. Biol. Med.* **2004**, *137*, 560–562. [CrossRef]
63. Nafiu, A.B.; Rahman, M.T. Anti-inflammatory and antioxidant properties of unripe papaya extract in an excision wound model. *Pharm. Biol.* **2015**, *53*, 662–671. [CrossRef]
64. Nafiu, A.B.; Rahman, M.T. Selenium added unripe *Carica papaya* pulp extracts enhance wound repair through TGF-β1 and VEGF-a signalling pathway. *BMC Complement. Altern. Med.* **2015**, *15*, 369. [CrossRef]
65. Collard, E.; Roy, S. Improved function of diabetic wound-site macrophages and accelerated wound closure in response to oral supplementation of a fermented papaya preparation. *Antioxid. Redox Signal.* **2010**, *13*, 599–606. [CrossRef]
66. Dickerson, R.; Deshpande, B.; Gnyawali, U.; Lynch, D.; Gordillo, G.M.; Schuster, D.; Osei, K.; Roy, S. Correction of aberrant NADPH oxidase activity in blood-derived mononuclear cells from type II diabetes mellitus patients by a naturally fermented papaya preparation. *Antioxid. Redox Signal.* **2012**, *17*, 485–491. [CrossRef] [PubMed]
67. Dickerson, R.; Banerjee, J.; Rauckhorst, A.; Pfeiffer, D.R.; Gordillo, G.M.; Khanna, S.; Osei, K.; Roy, S. Does oral supplementation of a fermented papaya preparation correct respiratory burst function of innate immune cells in type 2 diabetes mellitus patients? *Antioxid. Redox Signal.* **2015**, *22*, 339–345. [CrossRef] [PubMed]
68. Indran, M.; Mahmood, A.A.; Kuppusamy, U.R. Protective effect of *Carica papaya* L leaf extract against alcohol induced acute gastric damage and blood oxidative stress in rats. *West Indian Med. J.* **2008**, *57*, 323–326.
69. Nayak, S.B.; Pinto Pereira, L.; Maharaj, D. Wound healing activity of *Carica papaya* L. in experimentally induced diabetic rats. *Indian J. Exp. Biol.* **2007**, *45*, 739–743. [PubMed]
70. Gurung, S.; Skalko-Basnet, N. Wound healing properties of *Carica papaya* latex: In vitro evaluation in mice burn model. *J. Ethnopharmacol* **2009**, *121*, 338–341. [CrossRef] [PubMed]
71. Nayak, B.S.; Ramdeen, R.; Adogwa, A.; Ramsubhag, A.; Marshall, J.R. Wound-healing potential of an ethanol extract of *Carica papaya* (Caricaceae) seeds. *Int. Wound J.* **2012**, *9*, 650–655. [CrossRef]
72. Hakim, R.F.; Fakhrurrazi; Dinni. Effect of *Carica papaya* Extract toward Incised Wound Healing Process in Mice (Mus musculus) Clinically and Histologically. *Evid. Based Complement. Alternat. Med.* **2019**, *2019*, 8306519. [CrossRef] [PubMed]
73. Ajlia, S.A.; Majid, F.A.; Suvik, A.; Effendy, M.A.; Nouri, H.S. Efficacy of papain-based wound cleanser in promoting wound regeneration. *Pak. J. Biol. Sci.* **2010**, *13*, 596–603. [CrossRef]
74. Aravind, G.; Bhowmik, D.; S, D.; Harish, G. Traditional and medicinal uses of *Carica papaya*. *J. Med. Plants Stud.* **2013**, *1*, 7–15.
75. Murthy, M.B.; Murthy, B.K.; Bhave, S. Comparison of safety and efficacy of papaya dressing with hydrogen peroxide solution on wound bed preparation in patients with wound gape. *Indian J. Pharm.* **2012**, *44*, 784–787. [CrossRef]
76. Saha, S.K.; Lee, S.B.; Won, J.; Choi, H.Y.; Kim, K.; Yang, G.-M.; Dayem, A.A.; Cho, S.-G. Correlation between Oxidative Stress, Nutrition, and Cancer Initiation. *Int. J. Mol. Sci.* **2017**, *18*, 1544. [CrossRef] [PubMed]
77. Sosa, V.; Moliné, T.; Somoza, R.; Paciucci, R.; Kondoh, H.; Lleonart, M.E. Oxidative stress and cancer: An overview. *Ageing Res. Rev.* **2013**, *12*, 376–390. [CrossRef] [PubMed]
78. García-Solís, P.; Yahia, E.M.; Morales-Tlalpan, V.; Díaz-Muñoz, M. Screening of antiproliferative effect of aqueous extracts of plant foods consumed in México on the breast cancer cell line MCF-7. *Int. J. Food Sci. Nutr.* **2009**, *60* (Suppl. S6), 32–46. [CrossRef]
79. Zuhrotun Nisa, F.; Astuti, M.; Murdiati, A.; Mubarika Haryana, S. Anti-proliferation and Apoptosis Induction of Aqueous Leaf Extract of *Carica papaya* L. on Human Breast Cancer Cells MCF-7. *Pak. J. Biol. Sci.* **2017**, *20*, 36–41. [CrossRef]
80. Pathak, N.; Khan, S.; Bhargava, A.; Raghuram, G.V.; Jain, D.; Panwar, H.; Samarth, R.M.; Jain, S.K.; Maudar, K.K.; Mishra, D.K.; et al. Cancer chemopreventive effects of the flavonoid-rich fraction isolated from papaya seeds. *Nutr. Cancer* **2014**, *66*, 857–871. [CrossRef] [PubMed]
81. Somanah, J.; Ramsaha, S.; Verma, S.; Kumar, A.; Sharma, P.; Singh, R.K.; Aruoma, O.I.; Bourdon, E.; Bahorun, T. Fermented papaya preparation modulates the progression of N-methyl-N-nitrosourea induced hepatocellular carcinoma in Balb/c mice. *Life Sci.* **2016**, *151*, 330–338. [CrossRef]
82. Waly, M.I.; Al-Rawahi, A.S.; Al Riyami, M.; Al-Kindi, M.A.; Al-Issaei, H.K.; Farooq, S.A.; Al-Alawi, A.; Rahman, M.S. Amelioration of azoxymethane induced-carcinogenesis by reducing oxidative stress in rat colon by natural extracts. *BMC Complement. Altern. Med.* **2014**, *14*, 60. [CrossRef] [PubMed]
83. Murakami, S.; Eikawa, S.; Kaya, S.; Imao, M.; Aji, T. AntiTumor and Immunoregulatory Effects of Fermented Papaya Preparation (FPP: SAIDOPS501). *Asian Pac. J. Cancer Prev.* **2016**, *17*, 3077–3084. [PubMed]
84. Bussmann, R.W.; Malca, G.; Glenn, A.; Sharon, D.; Nilsen, B.; Parris, B.; Dubose, D.; Ruiz, D.; Saleda, J.; Martinez, M.; et al. Toxicity of medicinal plants used in traditional medicine in Northern Peru. *J. Ethnopharmacol.* **2011**, *137*, 121–140. [CrossRef] [PubMed]
85. Afzan, A.; Abdullah, N.R.; Halim, S.Z.; Rashid, B.A.; Semail, R.H.R.; Abdullah, N.; Jantan, I.; Muhammad, H.; Ismail, Z. Repeated dose 28-days oral toxicity study of *Carica papaya* L. leaf extract in Sprague Dawley rats. *Molecules* **2012**, *17*, 4326–4342. [CrossRef] [PubMed]
86. Halim, S.Z.; Abdullah, N.; Afzan, A.; Abd Rashid, B.; Jantan, I.; Ismail, Z. Acute toxicity study of *Carica papaya* leaf extract in Sprague Dawley rats. *J. Med. Plants Res.* **2011**, *5*, 1867–1872.
87. Tarkang, P.; Agbor, G.; Armelle, T.; Tchokouaha, L.R.; David, K.; Ngadena, Y. Acute and Chronic Toxicity Studies of the aqueous and ethanol leaf extracts of *Carica papaya* Linn in Wistar rats. *J. Nat. Prod. Plant Resour.* **2012**, *2*, 617–627.

foods

MDPI

Review

Benefits of Fermented Papaya in Human Health

Mariana Leitão [1,2,*], Tatiana Ribeiro [2], Pablo A. García [3], Luisa Barreiros [4,5] and Patrícia Correia [2,4]

1 Pharmacy Faculty, University of Salamanca, 37007 Salamanca, Spain
2 Research Centre on Health and Environment, Department of Pharmacy, School of Allied Health Sciences, Polytechnic Institute of Porto, 4200-072 Porto, Portugal; tatiribeiro96@gmail.com (T.R.); pcc@ess.ipp.pt (P.C.)
3 Department of Pharmaceutical Sciences, Pharmaceutical Chemistry Section, Faculty of Pharmacy, IBSAL, University of Salamanca, 37007 Salamanca, Spain; pabloagg@usal.es
4 School of Allied Health Sciences, Polytechnic Institute of Porto, 4200-072 Porto, Portugal; lsb@ess.ipp.pt
5 LAQV, REQUIMTE, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal
* Correspondence: marianaleitaofa@gmail.com

Abstract: Fermented foods have been used for several years all over the world, due to their unique nutritional characteristics and because fermentation promotes conservation and food security. Moreover, fermented foods and beverages have a strong impact on human gut microbiota. Papaya is the fruit of the *Carica papaya* plant, traditionally used as a medicinal fruit, but there are also references to the use of the fermented form of this fruit. The main purpose of this review is to provide an improved understanding of fermented papaya nutritional and health applications. A literature search was conducted in the PubMed and Google Scholar databases. Both in vitro and in vivo studies were included. According to the retrieved studies, fermented papaya has proven to be an excellent antioxidant and an excellent nutraceutical adjuvant in combined therapies against several diseases, such as Alzheimer's disease, allergic reactions, anticancer activity, and anemias. Therefore, it is concluded that fermented papaya has many benefits for human health and can be used as prevention or aid in the treatment of various diseases.

Keywords: fermented food; fermented papaya; health benefits; oxidative stress

Citation: Leitão, M.; Ribeiro, T.; García, P.A.; Barreiros, L.; Correia, P. Benefits of Fermented Papaya in Human Health. *Foods* **2022**, *11*, 563. https://doi.org/10.3390/foods11040563

Academic Editors: Wojciech Kolanowski and Anna Gramza-Michałowsk

Received: 31 December 2021
Accepted: 12 February 2022
Published: 16 February 2022

1. Introduction

Fermentation is a central metabolism process in which an organism, mainly yeasts and some bacteria, converts sugars and starches into alcohol (alcoholic fermentation) or carboxylic acid (lactic or acetic fermentation), oxygen-free or -limited conditions. During this conversion, an intermediate product is formed, for instance, pyruvate (or acetaldehyde), produced from glucose metabolism [1,2]. The most famous application of this process is in the field of food and nutrition.

Fermented foods are defined as foods and beverages produced by enzymatic reactions with controlled microbial growth, promoting conservation and food security [3]. Fermentation is a food-preserving method in many parts of the world, particularly in Asia and in Africa, because it inhibits the growth of pathogenic bacteria even without refrigeration or other preserving methods [3]. This process is also used in other contexts. For instance, in regions where the safety of water supplies cannot be assured, fermentation contributes to reduce the risk of waterborne diseases [4,5]. Fermentation also can improve food's organoleptic characteristics, such as taste and texture [3]. For example, olives are fermented to remove the bitter phenolic compounds [6]. Fermentation usually improves final foods' nutritional value in contrast to processing methods, such as pasteurization, commonly used in today's food industry. Fermented foods have a higher fiber content, essential fatty acids, amino acids, vitamins, and minerals [7].

Fermented products have been used for several years all over the world due to their nutritional characteristics, and there are several scientific evidences about the advantages of

fermented food. Fermented milk products, such as yogurt, have been recognized as healthy foods since ancient times [1], and although this kind of food has been consumed since the beginning of civilization, its popularity has increased in recent times, essentially due to its therapeutic potential. More than a century ago, the Nobel prize winner Elie Metchnikoff (1845–1916) affirmed that fermented food, such as yogurt, can increase health and delay senility [8]. Metchnikoff's concepts are currently supported by considerable evidence showing that lactic fermentation inhibits growth, survival, and production of toxins by some pathogenic and toxicogenic bacteria [9]. Another example is the consumption of an ancient Japanese fermented soy dish called natto that seems to increase vitamin K2 (menaquinone) concentrations in consumers, with several improvements in the health of the bones and heart [10]. Scientific evidence also suggests that the inclusion of fermented food in the diet can reduce the risk of cardiovascular disease [11] and the development of type 2 diabetes [7]. The National Institute of Nutrition's 2010 suggests in the "Dietary Guidelines for Indians" that pregnant women should eat more fermented foods [1].

Carica papaya, also known as papaya or pawpaw, belongs to the *Caricaceae* family that is divided into four genera spread around the world. The genus *Carica* Linn. is the most cultivated and best-known species [12,13]. The papaya taxonomical classification includes kingdom (*Plantae*); order (*Brassicales*); family (*Caricaceae*); genus (*Carica*); and species (*Carica papaya*) [13]. Papaya was also named as "the fruit of the angels" by Christopher Columbus or as "a fruit of long life" [12]. Papaya is believed to be native to southern Mexico and neighboring Central America. It is currently widely planted in Brazil, Hawaii, Florida, South Africa, India, Australia, and others. Brazil is the leading world producer, with papaya as its most economically relevant fruit within the *Caricaceae* family [14].

Papaya's main carbohydrates are simple sugars, as in ripe papaya, which contains 48% (*w*/*w*) sucrose, 30% (*w*/*w*) glucose, and 22% (*w*/*w*) fructose [14]; but the fruit is also rich in food fibers, which increases intestinal motility, which is enhanced with papain enzyme when it is present in large quantities [15]. Papaya contains a broad spectrum of phytochemicals, including enzymes (in latex), alkaloids (in leaves), phenolic compounds (in pulp and leaves), and carotenoid compounds and glucosinolates (in pulp and seeds). This fruit also contains large amounts of the least active pro-vitamin A, β-cryptoxanthin [16], and other micronutrients, such as sodium, calcium, phosphorus, zinc, iron, copper, and manganese, in a considerable amount [17]. For instance, in addition to phenolics (for example, vitamin K) and carotenoids (specifically pro-vitamin A), papaya's pulp is also rich in magnesium, potassium, ascorbic acid (vitamin C), vitamin E, and B complex vitamins (such as pantothenic acid and folate). Lycopene, the main pigment in red pulp papaya, has important health implications as a strong antioxidant due to its great capacity for scavenging free radicals among carotenoids, closely followed by β-cryptoxanthin and β-carotene [18]. Seeds are rich in phenolic compounds, including benzyl isothiocyanate, glucosinolates, β-carotene, and carotenoids [19,20]. In terms of organic acids present in papaya, there is almost the same amount of malic and citric acids and smaller amounts of ascorbic acid and α-ketoglutaric acid [21]. It is recognized that there are some factors affecting papaya's content: carotenoid and ascorbic acid content increase with ripeness; longer day lengths and higher light intensities in summer can increase fruit's concentrations of ascorbic acid and its precursor, glucose [18]. Different parts of papaya have been used in folk medicine to treat various diseases, especially diabetes, cancer, and cardiovascular and infectious diseases. Some studies also show that papaya can also be used to prevent sickle cell anemia [22]. Carotenoids, phenolic compounds, and glucosinolates have attracted considerable interest in anticancer studies. These compounds may act via multiple mechanisms, such as cancer cell signaling, proliferation, apoptosis, migration, invasion, as well as angiogenesis and carcinogen elimination [23,24]. Usually, only papaya pulp is consumed, and ripe fruit is a carminative, diuretic, expectorant, sedative, and has preventive action against dysentery, skin diseases, psoriasis, and ringworm. The unripe fruit is used as a remedy for ulcers and impotence, reducing menstrual irregularities, and promoting natural menstruation flow in women [25]. The low-calory content (32 kcal/100 g of ripe fruit) and

high nutritive value make papaya a preferred and excellent dietary product for weight-reducing regimes and diabetic patients [17]. Papaya juice helps in relieving colon infections and gastrointestinal maladies, such as dyspeptic and celiac disease, whose patients cannot digest wheat protein gliadin but can tolerate it if treated with crude papain [25]. In fact, two important compounds of papaya are chymopapain and papain, which are widely useful for digestive disorders and disturbance of the gastrointestinal tract. Physicochemical characterization and fatty acid composition analysis of crude oil extracted from papaya seeds showed high content of unsaturated fatty acids (78.17%), most of them monounsaturated fatty acids (71.89%). Therefore, papaya seed oil has a beneficial monounsaturated fatty acid profile and may have potential use in nutrition. Additionally, papaya seeds can also have another nutritional added value because they are a rich source of proteins (27.3–28.3%), lipids (28.2–30.7%), and crude fibers (19.1–22.6%) [26]. Furthermore, lipids with high monounsaturated fatty acid content are used in emollient skincare products, such as bath oils, hair conditioners, and makeup, which enhances seed oil potential in pharmaceuticals, specifically in dermo-cosmetics [26]. Both seed coat and papaya oil possess reasonable antioxidant properties, which emphasizes their nutritional potential and health benefits. The oil could also be useful for biofuel purposes, and seed coat may be used in the development of edible coating or packaging materials [27]. Papaya latex is very useful for healing dyspepsia, diarrhea, bleeding hemorrhoids, and whooping cough, and it is also externally applied to treat skin burns [17]. The green leaves of the tree are a source of essential nutrients, while the yellow ones provide mostly iron, which means that they can be used against anemia, tuberculosis, and growth disorders. It is also described that leaves with high iron content may have a synergistic action to reduce enlarged spleen and liver, and they are used to remove snakebite poison [17]. Malaria is also treated by using papaya leaves in some countries, such as Indonesia [28], probably related to the presence of antiplasmodial alkaloids in the leaves [29]. Leaves have also an important role in blood coagulation, the functioning of the heart and nervous system, and normal muscles movement [30]. Papaya leaves have also shown anti-hyperglycemic and hypolipidemic effects. A study carried out to evaluate the hypoglycemic effect of the aqueous extract of papaya leaves in streptozotocin-induced diabetic rats showed that there was a significant decrease in body weight in diabetic rats. After the administration of different doses of the aqueous extract of papaya to diabetic rats for 30 days, a significant decrease in blood glucose levels was observed. Moreover, significant decreases in serum cholesterol and triacylglycerol levels were observed in comparison to untreated diabetic rats after a 4-week administration of 3 g/100 mL of papaya leaf extract to diabetic rats [31]. The whole plant has high medicinal value as a result of its broad spectrum of vitamins, enzymes, and other active compounds [13].

Due to the already reported and numerous benefits of papaya and to the growing offer of different supplement brands with fermented papaya, such as the Fermented Papaya Product® (FPP®), it is relevant to recognize the important of fermented papaya in human health. FPP® is owned by Osato Research Institute in Japan and sold under the commercial name Immun'Âge®. This product is made with non-genetically modified *Carica papaya* and follows food safety standards (ISO 9001: 2000, ISO 14001: 2004, and ISO 22000: 2005). The final product is sold in granulated form. FPP® is commercialized as a functional food in several countries (Japan, United States, and some European countries). FPP® is made with wild, unripe *Carica papaya* Linn. fermented with *Enterococcus faecalis*, followed by fermentation with *Aspergillus oryzae*. These processes are performed at room temperature under aerobic conditions [8]. The therapeutic activity of FPP® may be due to the formation of new bioactive compounds resulting from the fermentation process. With fermentation, polyphenols are converted into compounds of lower molecular weight and, consequently, with enhanced therapeutic activity [32,33]. In fact, the chemical analysis by spectroscopy and chromatography methods revealed the presence of low molecular weight phenolic acids (quinic acid, shikimic acid, and 2,5 dihydroxybenzoic acid) in fermented papaya [34].

Thus, the primary aim of this review is to provide an improved understanding of fermented papaya nutritional and health applications described in the literature.

2. Materials and Methods

Data were gathered from February to March 2021, using PubMed and Google Scholar databases, with the search terms "fermented papaya", "Fermented Papaya Preparation", "FPP®", "Fermented papaya extracts", "*Carica papaya*", "Papaya", "fermented food", "fermented fruit", and "fermented preparation". The search was also carried out with the same search terms in Portuguese, but no further results were found. The articles admitted for analysis were published during the last twenty years, and included clinical studies (in vivo, in vitro, observational studies), review articles, and case reports, all of them in the English language. All abstracts were read in order to exclude the articles that were out of the scope of this study's subject. The remaining articles were fully read, and then, data were collected, dividing the main subject into four categories: immunomodulatory, antioxidant, and anticancer properties; congenital/acquired hemolytic anemias; antidiabetic and antidislipidemic properties; and skin benefits and wound-healing properties.

3. Results and Discussion

Most studies on fermented papaya focus on its immunomodulatory, antioxidant, anticancer, and anti-inflammatory properties. However, there are also many studies that mention its antidiabetic and antidislipidemic properties and even its usefulness in anemias. Fermented papaya can also be applied in the dermo-cosmetic area due to its skin benefits.

3.1. Immunomodulatory, Antioxidant and Anticancer Properties

The main immunomodulatory, antioxidant, and anticancer effects of the fermented papaya are summarized in Table 1.

Table 1. Immunomodulatory, antioxidant, and anticancer properties of fermented papaya.

Preparation	Study Type	Dose	Model	Bioactive Effect	Reference
FPP®	In vitro study	3 mg/mL	Murine monocyte/macrophage cell line RAW 264.7 treated with IFN-γ and/or FPP®	FPP fractions in the presence of IFN-γ both LMF and HMF: ↑ iNOS activity ↑ nitrate and nitrite accumulation	[35]
FPP®	In vitro study	1.2, 2.4, 4.8 mg/mL	AD cell model	Attenuated the Aβ neurotoxicity and prevents the cell apoptosis ↓ ROS ↓ accumulation of intracellular NO ↓ iNOS	[36]
FPP®	Randomized, Placebo-Controlled, Cross-Over Study	Group A: 9 g/day Group B: placebo (3 months)	54 elderly patients randomly divided into 2 groups (Group A and B)	FPP® supplemented group: ↑ antioxidant protection	[37]
FPP®	Pilot study	6 g/day	11 healthy nonsmoker patients	Plasma level of the tested redox parameter did not change ↓ nonsignificant decrease of MDA upregulation of all gene expression investigated	[38]
FPP®	In vivo study	6 mg/mouse/day	Specific pathogen-free male ICR mice with 8 weeks old	↓ contact hypersensitivity ↓ IFN-γ, IL-10, and TNF-α ↓ IgA and dendritic cells	[39]
FPEs	In vivo study	5–30 mL FPEs/kg (1 month)	36 female mice divided into 6 groups	Protective effect of FPEs on mammary gland pathology in model animals: ↑ SOD and GSH-Px ↓ MDA	[40]

Table 1. *Cont.*

Preparation	Study Type	Dose	Model	Bioactive Effect	Reference
FPEs	Clinical study	Group A: control group Group B: 3 g/day Group C: 9 g/day (1 month)	4 males and 8 females with cerebrovascular disease, 4 males and 3 females with neurodegenerative disease, and 1 male post-traumatic head injury divided into 3 groups	↑ PBMC cytolytic activity ↑ NK cell cytotoxicity ↓ *Firmicutes*, *C. scindens*, and *E. lenta* ↓ offensive fecal odor	[41]
FPP®	In vivo study	50 mg/mouse/day (5–7 months)	SHR	↓ MC- PROXYL ↑ redox defense activity in SHR brain	[35]
FPP®	In vivo study	150, 300, or 450 mg/kg/day (oral administration)/ 1600 or 4000 mg/kg/2 days (intraperitoneal injection)	Mouse cancer model	Oral administration of FPP inhibited tumor growth	[42]
	In vitro study	10 mg/mL	PBMC	↑ IL-1β, TNFα and IFNγ	
FPP®	In vivo study	200, 400 mg/kg/day	35 mice cancer models divided into 7 groups	↓ tumor mass of about three to seven times vs. untreated mouse; ↓ ROS ↑ antioxidants (SOD-1 and GSH)	[43]
FPP®	In vivo study	6 mg/mouse/day	40 aging female mice model divided into 2 groups	↑ telomerase activity ↓ ROS ↑ antioxidants	[44]

Aβ, substance β-amyloid; AD, Alzheimer's disease; FPEs, fermented papaya extracts; GSH, free glutathione; GSH-Px, glutathione peroxidase; HMF, high molecular fraction (FPP®); IFN-γ, interferon- γ; IL-1β, interleukin-1β; iNOS, nitric oxide synthase; LMF, low molecular fraction (FPP®); MG, methylguanidine; NO, nitric oxide; PBMC, human peripheral blood mononuclear cells; ROS, reactive oxygen species; SHR, spontaneously hypertensive rats; SOD, superoxide dismutase; SOD-1, enzyme superoxide dismutase-1; TNF-α, tumor necrosis factor-α. ↑ increase, ↓ decrease.

A study performed with FPP® showed that this product has immunomodulatory and antioxidant properties in macrophages cell line RAW 264.7. When cells are treated only with FPP® extracts, no significant differences in nitric oxide production are observed. However, when cells had been previously treated with interferon-γ (IFN-γ), both low molecular weight and high molecular weight FPP® extracts increased the enzyme iNOS (nitric oxide synthase) activity, also increasing levels of nitrite and nitrate. Besides, when IFN-γ is present, the low and high molecular weight FPP® extracts stimulate the secretion of tumor necrosis factor-α (TNF-α). It was also observed that the low molecular weight FPP® extract has a greater capacity to scavenging superoxide anions when compared to high molecular weight FPP® extract [35]. These results may indicate that FPP® could act as a macrophage activator because of its augmentation on nitric oxide synthesis and on TNF-α secretion.

It is known that the deposition of the substance β-amyloid (Aβ) is related to Alzheimer's disease development although its exact action mechanisms are not yet well defined. Studies show that there may be an association between free radicals and the development of Alzheimer's disease. Hence, due to its antioxidant properties, the effect of FPP® on reducing the Aβ associated with Alzheimer's disease was evaluated by Zhang and collaborators (2006). In their analysis, a model of cellular Alzheimer's disease was used by using copper to trigger the neurotoxicity of Aβ. About the accumulation of reactive oxygen species (ROS), copper increased the ROS generation that was eliminated when cells were post-treated with FPP®, protecting the cell from the Aβ neurotoxicity. This treatment also decreased the lipid peroxide level and the accumulation of intracellular nitric oxide (NO). These authors found that FPP® can improve antioxidant effect in vivo and in vitro by increasing free radical scavenging. FPP® has also decreased the accumulation of ROS and NO. In fact, FPP® can improve Aβ neurotoxicity impaired by copper and prevent cell apoptosis [36].

Marotta and co-workers (2006) conducted a placebo-controlled and randomized cross-over study to examine the FPP® effects on redox activity and DNA damage in a healthy

elderly population. The elderly population has less antioxidant capacity due, for example, to nutritional deficits, reduced nutritional intake, and failures in intestinal absorption. Dietary antioxidants can reduce DNA adducts depending on the detoxifying activity of GSTM1 isoenzyme. Therefore, these authors analyzed the polymorphism of GSTM1 (glutathione S-transferase M1) in 54 elderly individuals. One group was orally supplemented with FPP® (9 g/day), and the control group received the same amount of placebo (flavored powdered sugar) for three months, followed by a six-week washout period. The FPP® oral supplemented group showed a significant enhancement of the antioxidant protection in the GSTM1 negative subgroup regardless of smoking ($p < 0.01$). It was also observed that FPP® exerts protective effects on leukocyte DNA adducts formation irrespective of genotype profile. Additionally, FPP® oral supplementation can enhance DNA repair mechanisms but only in GSTM1-null genotype patients. These results showed that FPP® can improve antioxidant activity in elderly individuals even without any overt antioxidant deficiency state [37]. In order to continue the previous study's conclusions, Marotta and his colleagues (2010) studied the effect of FPP® on redox balance gene expression in 11 healthy non-smoker subjects. All patients were sublingually supplemented with FPP® 6 g/day, and the blood was collected at the second and fourth weeks of observation. The researchers analyzed the antioxidant enzyme activity, lipid peroxidation, and protein oxidation. They observed that the plasma level of the tested redox parameter was unchanged, but FPP® significantly upregulated all tested gene expression ($p < 0.05$) [38]. These results, although preliminary, indicate the nutrigenomic potential of FPP®.

The effect of FPP® on the type IV allergic reactions in skin and intestine was investigated by Hiramoto and his colleagues (2008). Th1-dependent type IV and Th2-dependent mucosal allergic reactions were elicited in the skin and intestine of male ICR mice by repeated sensitization with oxazolone and fluorescein isothiocyanate (FITC), respectively.

In this study, it was observed that plasma levels of IFN-γ, IL-10, and TNF-α, measured by ELISA, increase either FITC or oxazolone sensitization and that, after FPP® administration, they were reduced. Both FITC and oxazolone increased ear and colon thickness at 24 h after the challenge. After either the FITC or oxazolone challenges, the colonic expression of IgA markedly increased, but there was a little expression in the FPP®-treated animals in comparison to the dextrose-treated animals. Biochemical analyses revealed that the FPP® decreased ear swelling, inflammatory cytokine levels in plasma, and IgA, dendritic cells, and inflammatory cells expression in colon [39]. These results suggest that FPP® may have therapeutic potential for the prevention of contact hypersensitivity.

Mammary gland hyperplasia is a common noninflammatory and nontumor disease that occurs in women of child-bearing age. This condition accounts for 75% of all breast diseases. The occurrence of mammary gland hyperplasia is directly related to endocrine disorders, which are mainly caused by an imbalance of estrogen and progestin. Accordingly, a study investigated the protective effect, functions, and action mechanism of Fermented Papaya Extracts (FPEs) obtained through *Aspergillus* and yeast long-term fermentation in estrogen-induced mammary gland hyperplasia. The study was performed using 36 female rats divided into six groups: the blank control group, the FPEs control group, the model group (that received an intramuscular injection of estradiol benzoate and of progestin), and the three treatment groups (that received estradiol benzoate and progestin equal to the model group and were treated orally with FPEs in three different concentrations). After 30 days, the right nipple of the rats in each group was shaved for the measurement of the diameter and height. Blood and tissue samples were collected from the mammary glands, heart, liver, spleen, lung, kidney, ovary, and uterus, and the concentration of each sex hormone (estradiol, progesterone, luteinizing hormone, and follicle-stimulating hormone) was analyzed. Histopathological analysis showed that the blank control group and the control group administered with only FPEs showed no apparent hyperplasia. Instead, severe pathological changes (mammary gland hyperplasia, lobule increase, acinar increase, mammary duct and lumen ectasia, and mammary duct and lumen secretion increase) were observed in the model group. Analysis of oxidant levels showed that FPEs may increase

superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities and decrease malondialdehyde (MDA) [40]. The results indicated that FPEs can increase the antioxidant levels and inhibit the hyperplasia of mammary glands by antioxidants and prevent liver damage via their antioxidant properties.

Fujita and his collaborators (2017) examined the effects of FPEs supplementation for 30 days on immunological and metabolic functions and fecal flora in tube-fed patients. Study participants were divided into three groups: a control group (that did not receive FPE), and two treated groups (administered with 3 g FPE per day or 9 g FPE per day). Elderly patients who are long-term tube-fed have decreased peripheral blood mononuclear cell (PBMC) cytolytic activity. Administration of FPE at 3 and 9 g per day restored PBMC cytolytic activity, significantly increased NK cell cytotoxicity in a dose-dependent manner, and did not affect IgG, IgA, and IgM levels. Analysis of fecal samples at the beginning of the study, in the control group, and also in the FPE groups showed characteristic microbiota with a high proportion of phylum *Firmicutes* and genus *Parabacteroides* and with a low proportion of genus *Bifidobacterium*. Administration of FPE at 9 g per day reduced the abundance of *Firmicutes*, *Clostridium scindens*, and *Eggerthella lenta*, and the fecal odor [41].

Yoshino and co-workers (2009) investigated the ability of long supplementation (5–7 months) of FPP® to modulate oxidative stress following the electron spin resonance images of the 3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine-1-oxyl (MC-PROXYL). The supplementation with FPP® led to a rapid decay of MC-PROXYL in the spontaneously hypertensive rat (SHR) brain. The decay rate constant of MC-PROXYL in the isolated brains of SHR is increased in the brain of normal male Wistar Kyoto rats. Supplementation with FPP® increased the decay rate constant of MC-PROXYL in the isolated brains of SHR. This appears to indicate that FPP® up-regulated antioxidant activity in the SHR brain. It can be concluded that FPP® has protective effects against oxidative injury, supporting the view that prophylactic potentials in chronic degenerative diseases and particular diseases of overt inflammation [35].

Another study from Murakami and collaborators (2016) analyzed FPP® effects in carcinogenesis in vivo and immunomodulatory function in vitro. They reported an anti-tumor effect of FFP® in vivo using mouse cancer models. Oral administration of FPP® inhibited tumor growth, and a dose of 450 mg/kg/day eliminates the tumor. Interleukin-1β (IL-1β), TNFα, and IFNγ, released by immunocytes, participate in numerous immunological and inflammatory reactions and can inhibit tumor progress. Thus, this work stated that FPP® can activate innate immunity and has chemotherapeutic properties, by stimulating IL-1β, TNFα, and IFNγ released in vitro. The authors also observed that oral administration of FPP® inhibited tumor evolution in mouse cancer models in a dose-dependent manner. Additionally, oral administration of FPP® a dose of 450 mg/kg/day results in complete disappearance of the tumor. However, these results were only observed after oral but not intraperitoneal administration [42]. This may happen due to FPP® metabolism and interactions with microflora.

A recent in vivo study by Logozzi and co-workers (2019) reported that FPP® can control murine melanoma tumor growth and reduce a tumor mass of about 3–7 times versus untreated mice. They verified that the optimal effect of FPP® on tumor growth was with a dose of 200 mg/kg/day. They also demonstrated a decrease in the blood total ROS levels and an increase in levels of antioxidants free glutathione (GSH) and enzyme superoxide dismutase-1 (SOD-1). These results are promising in tumor prevention and antioxidant effects [43]. These results show great perspectives and can lead to new studies about FPP® as an anticancer agent.

Another recent study from Logozzi et al. (2020) suggested the FPP® has anti-aging and antioxidant effects. Mice were daily treated with FPP® and compared with mice receiving only tap water. After ten months of the FPP® treatment, it was shown that FPP® induced an increase in telomeres length in bone marrow and ovary. Beyond this, they also caused an increase in the plasmatic levels of telomerase activity and the antioxidant levels. This study has also evaluated the FPP® effect on redox balance, with a decrease of ROS, and

with an anti-aging effect, as shown by the length of telomeres and telomerase quantification in FPP®-treated mice. This study also showed that FPP® was more effective when it starts at an early age as compared to late treatment. The results suggest also that FPP® treatment may extend the fertility period at least in the females, suggesting that the use of FPP® may be helpful in preventing or treating female infertility [44].

In general, fermented papaya has the ability to modulate the immune system and exhibits antioxidant activity, being able to reduce ROS, but also improves redox balance and boosts natural defense mechanisms of the immune system. Fermented papaya has also shown the capacity to inhibit tumor growth. Fermented papaya's antioxidant activity may be attributed to its polyphenolic content. However, as a natural product, the active compounds responsible for the described benefits may vary due to several reasons, such as the fruit cultivation conditions (country, temperature, and soil quality) and the fermentation protocol (temperature, duration, and used strains). In addition, it is reported that fermented papaya has low molecular weight oligosaccharides different from fresh fruit, which may be responsible for the immunomodulatory activity of fermented papaya [45].

3.2. Congenital/Acquired Haemolytic Anemias

The results of the studies regarding fermented papaya health benefits in congenital/acquired hemolytic anemias are summarized in Table 2.

Table 2. Fermented papaya health benefits in congenital/acquired hemolytic anemias.

Preparation	Study Type	Dose	Model	Bioactive Effect	Reference
FPP®	In vitro study	10 mg/mL	Normal and thalassemic RBC	↑ glutathione content of RBC, platelets, and PMN leukocytes ↓ ROS and membrane lipid peroxidation	[42]
	In vivo study	50 mg/mouse/day (3 months)	β-thalassemia mice models		
	Observational study	3 g 3 times/ day (3 months)	8 patients with β -thalassemia intermedia and 3 with β -thalassemia major		
FPP®	Observational study	3 g 3 times/day	β- thalassemia group (8 patients with β-thal intermedia and 3 with β-thal major)	↑ GSH ↓ ROS; membrane lipid peroxidation	[43]
		3 g 2 times/day	E-β- thalassemia group (7 patients)		
FPP®	Case report	3 g 3 times/day (4 months)		↑ Hb level ↓ LDH and Malondialdehyde ↓ patient fatigue ↑ patient performance	[44]
FPP®	In vitro study	Incubation of HS-RBC for 2 h with 0.1 mg/mL	HS-RBC from 17 patients	↑ Hb level ↓ Malondialdehyde ↓ ROS ↑ GSH	[45]
	In vivo study	3 g 3 times/day (3 months)	10 (8 males and 2 females) HS patients		

FPPP®, fermented papaya preparation; GSH, reduced glutathione; Hb, free hemoglobin; HS, hereditary spherocytosis; LDH, lactate dehydrogenase; PMN, polymorphonuclear; RBC, red blood cells; ROS, reactive oxygen species. ↑ increase, ↓ decrease.

Thalassemias are a group of inherited diseases that lead to malfunctioning hemoglobin production. Patients with thalassemia have a mutation that causes inefficient erythropoiesis [46]. Iron-induced toxicity in β-thalassemia is the most important cause of oxidative stress [47]. Data from some studies suggest that FPP® has antioxidant properties that may have some benefit in hemoglobinopathies, such as β thalassemia. In a study that was set out to determine the FPP® effect in β-thalassemia, Amer and his colleagues analyzed the antioxidant effects of FPP® in vitro and in vivo on red blood cells (RBC), platelets, and polymorphonuclear of β-thalassemia mice and patients. For this, mice were treated orally with FPP® (50 mg/mouse/day for three months) and 11 patients (eight β-thalassemia intermedia and three β-thalassemia major) with 3 g of FPP® three times a day during

the same period. The current study started to find that in vitro FPP® treatment reduced thalassemic red blood cell sensitivity to hemolysis and phagocytosis, improved polymorphonuclear ability to generate oxidative burst, and reduced platelet tendency to undergo activation. Furthermore, the researchers studied FPP® in vivo effect in thalassemic mice and observed that treatment with FPP® significantly reduced all tested oxidative stress parameters. Finally, they studied the FPP® effect in patients, and like the results obtained in vitro, these results showed a significant reduction in all oxidative stress parameters tested in blood cells [48]. Another study conducted by some authors of the previous study investigated the effect of oral supplementation with FPP® in oxidative status of two groups of thalassemia patients: β-thalassemia major and intermedia (in Israel) and E-β-thalassemia (in Singapore). The researchers reported that oral supplementation with FPP® showed a significant decrease in all oxidative stress parameters tested in their RBC [49]. The evidence presented before suggests that FPP® has a potent antioxidant power and might relieve symptoms associated with oxidative stress in severe forms of thalassemia. The antioxidant effect of FPP® in reducing oxidative stress biomarkers in these studies is undetermined although one possible justification could be its high content of glutamic acid, glycine, and methionine, which are substrates for reduced glutathione (GSH) production [44]. Despite this, both previous studies showed no significant improvement in the hematological parameters [43,44].

A report analyzed by Ghoti and his colleagues presents a clinical case regarding a patient with paroxysmal nocturnal hemoglobinuria, an acquired blood disease characterized by intravascular hemolysis, which is the main cause of anemia. After oral supplementation with FPP® (3 g, 3 times/day, for 4 months), this patient's free hemoglobin (Hb), white blood cell, and all other hemolytic parameters levels increased. They also described a significant decrease of the malondialdehyde level (a product of lipid membrane peroxidation). Overall, there seems to be some evidence that FPP® treatment has an antioxidant effect and seems to benefit in paroxysmal nocturnal hemoglobinuria [50]. Following up on the discoveries of the previous report and to better understand the FPP® antioxidant effect in hemoglobinopathies, Ghoti and his colleagues developed an in vivo and in vitro study to evaluate the FPP® effect in hereditary spherocytosis (HS). The in vitro study was performed with RBC from seven HS patients. They treated RBC-HS with FPP® (0.1 mg/mL for 2 h) and observed significantly reduced oxidate stress markers, such as a decrease in ROS, an increase in reduced glutathione, and less hemolysis in RBC treated with FPP®. The in vivo study included ten patients with mild to severe HS and supplemented them with 3 g of FPP® 3 times/day for 3 months. After 3 months, FPP® increased hemoglobin levels from 11.2 to 12.4 g/dL and mean corpuscular hemoglobin concentration decreased from 34.5 to 33.4 g/dL. They also verified a significant decrease in lactate dehydrogenase from 550 to 458 U/L [51]. Thus, these series of promising results suggest FPP® has a potent antioxidant effect, which can relieve symptoms associated with oxidative stress in both congenital and hemolytic anemias [44–46].

In line with the previous topic, FPP® reduces oxidative stress, decreases ROS, and improves immune system defenses. FPP® can protect red blood cells, which therefore improves hemolytic parameters and may be useful in the treatment/control of symptoms of congenital or hemolytic anemia. This health benefit can be justified based on the nutritional richness of papaya in vitamins or minerals.

3.3. Antidiabetic and Antidislipidemic Properties

Diabetes mellitus is a metabolic disease described by hyperglycemia and insufficiency of insulin. Oxidative stress is considerable as an important contributing factor in the pathogenesis of type 2 diabetes by an excess of ROS and glucose autoxidation [52]. Danese and his colleagues (2006) showed that oral supplementation with FPP® causes a significant decrease in plasma glucose levels in both healthy and type 2 diabetes patients. As such, they divided 50 individuals into two groups: a group of 25 patients diagnosed with type 2 diabetes mellitus undergoing pharmacological treatment with an oral antidiabetic

and a control group of 25 healthy people. All individuals were supplemented with oral FPP® (3 g/day) for three months. They observed a hypoglycemic effect in both groups, concluding that FPP® can be used as an adjunct therapy in type 2 diabetes mellitus [53].

Additionally, FPP® supplementation improved the blood lipid profile: total triglycerides, total cholesterol, and low-density lipoproteins levels decreased significantly ($p < 0.05$), while high-density lipoproteins levels (HDL) increased [54]. In fact, intake of individual antioxidants has been related to a lower risk of type 2 diabetes [55]. In addition, intake of carotenoids, such as β-carotene, has been reported due to the ability to reduce type 2 diabetes risk [56]. Carotenoids, which are widely present in papaya, might play a role in the treatment of diabetes mellitus and its side effects. Most reliable studies confirm that there is an inverse correlation between the plasma carotenoid concentration and diabetes mellitus incidence [57]. Furthermore, as oxidative stress is present in diabetes (due, for example, to glucose autoxidation), the antioxidant capacity of fermented papaya appears to have a protective action. Oxidative stress is increased in diabetes by the glucose auto oxidation and low levels of antioxidants. Thus, oxidative stress contributes to diabetes or its resulting complications. As fermented papaya exhibits antioxidant properties, it permits to reduce oxidative stress and therefore controls diabetes and even other dyslipidemias.

3.4. Skin Benefits and Wound-Healing Properties

The results of the studies regarding the fermented papaya health benefits in skin and wound-healing properties are summarized in Table 3.

Table 3. Fermented papaya skin benefits.

Preparation	Study Type	Dose	Model	Bioactive Effect	Reference
BioRex®	In vitro study	1–5 mg/mL	Peripheral blood neutrophils	Suppressed generation of superoxide, hydroxyl radical, and total production of radicals; ↓ catalase activity	[58]
	In vivo study	-	Thermal wound model in rats	↓ wound area and bacterial burden; ↓ catalase activity	
FPP®	In vivo study	FPP group: 0.2 g/kg 5 days/week (8 weeks) Placebo group: D-glucose in the same manner as in FPP group (8 weeks)	Adult obese diabetic mice divided into 2 groups (FPP and placebo control)	↑ NO and iNOS	[54]
FPP®	Double-blind study	FPP group: 4.5 g 2 times/day (90 days) Antioxidant control group: Antioxidant cocktail with similar flavored and in the same manner as in FPP group (90 days)	60 healthy non-smoker males and females (40–65 years) divided into 2 groups	FPP supplementation: ↑ skin moisturization, evenness, and elasticity; ↑ NO and SOD production; Gene regulatory improvement in the skin.	[59]

FPP®, fermented papaya preparation; NO, nitric oxide; SOD, superoxide dismutase. ↑ increase, ↓ decrease.

Mikhal and co-workers (2004) conducted a study to evaluate in vivo and in vitro wound-healing effect of the preparation from fermented papaya sold as BioRex®. They induced burn trauma in Wistar rats (burns IIA-B-20% of skin area) and evaluated the effects of the preparation from fermented papaya. The control group was treated with paraffin gauze dressings. The antioxidant effect of BioRex® in skin was tested in vitro, analyzing the formation of the hydroxyl and superoxide radicals (H_2O_2—$FeSO_4$) and xanthine (xanthine oxidase model), and there was an observed antioxidant effect on treated cells (human peripheral blood neutrophils). In vivo studies (thermal wound model in rats), with BioRex® topical treatment reduced the wound area and bacterial burden (*Staphylococcus aureus*) by lowering their catalase level. This study also revealed considerable differences in the rate of wound healing with BioRex® when comparing treated and control rats on day 8 of

the experiment. On day 12 after trauma, the wound area in BioRex®-treated rats was two-fold lower than in control animals. The results suggest that local treatment with the preparation from papaya accelerates wound healing in rats with burn trauma. This preparation decreased the production of free radicals in the whole blood of animals, which reflects changes in the general inflammatory reaction related to the indirect antibacterial effect and antioxidant properties [58]. The beneficial actions of papaya on the skin may be also due to the presence of enzyme papain that may facilitate wound debridement [60].

Collard and Roy (2010) studied the effects on wound healing in adult obese diabetic mice. FPP® supplementation significantly improved wound healing in diabetic mice. They also verified an improved nitric oxide production by wound macrophages and elevated iNOS gene expression in wound tissue in FPP®-supplemented diabetic mice. It is known that in diabetes, there is a deficit of NO in the wound site, and it is also known that NO is involved in wound healing through multiple modes of action. Hence, an increase in NO delivery by FPP® has a beneficial effect on diabetic wound healing [54]. These results confirm the previously reported study from Danese and his colleagues (2006). In fact, recent research has shown that oral supplementation with FPP® causes a decrease in plasma sugar and improves the blood lipid profile [53]. It is also known that oxidative stress is increased in diabetes by glucose autoxidation and low levels of antioxidants [61].

A double-blind study aimed to compare the skin anti-aging effect of oral supplementation between FPP® and an antioxidant cocktail (10 mg trans-resveratrol, 60 µg selenium, 10 mg vitamin E, and 50 mg vitamin C). For this study, 60 healthy non-smoking individuals between 40 and 65 years old with clinical signs of skin aging were recruited. In the FPP®-treated group, patients were sublingually supplemented with 9 g/day (4.5 g × 2 times/day). In the antioxidant control group, patients received an antioxidant cocktail in the same way as in the other group. In both groups, the FPP® and the antioxidant cocktail administration was performed for 90 days. The authors measured parameters, such as skin moisturization, skin elasticity, skin surface, brown spot intensity, skin gene expression, dermal redox balance, and nitric oxide assessment. They observed that FPP® can increase skin moisturization after 90 days (~95% increase; $p < 0.04$), and the antioxidant cocktail did not change this parameter. The overall evenness was assessed as significantly enhanced in the FPP®-treated group ($p < 0.05$) but not in the antioxidant-control group. Both FPP® and antioxidant cocktail improved the malondialdehyde and superoxide dismutase skin levels, but only the FPP®-treated group exhibited a higher superoxide dismutase level and a significant nitric oxide rise. They also observed a significant upregulation of defensive genes and downregulation of the potentially pro-aging/carcinogenic genes [59].

In accordance with previous sections, the high antioxidant power of fermented papaya, its anti-inflammatory capacity, and the ability to reduce free radicals have proved to be useful on skin, specifically in wound healing. Chronic wounds in patients with diabetes represent a major public health problem. Macrophages at the wound site of patients with diabetes are compromised in their ability to support wound healing. Fermented papaya may improve diabetic wound outcomes by specifically influencing the macrophage response at the wound site and subsequent angiogenic response. In addition, fermented papaya is also useful in hydrating the skin. This fact, combined with its antioxidant properties, shows that fermented papaya can be an excellent natural anti-aging agent.

4. Conclusions

Fermented papaya is recognized as a nutraceutical with an exceptionally diverse composition. Although only the pulp of the fruit is consumed, both the peel and the seeds of the papaya have a great phytochemical value, so they should not be wasted. Several experiments to determine its biological activity were carried out. Several studies have proven its anti-inflammatory, immunomodulatory, anticancer, and antioxidant physical activities. Intake of antioxidants and nutraceuticals reduces oxidative stress and can help mitigate and prevent various illnesses, such as Alzheimer's disease and dementia. Fermented papaya has several health benefits, highlighting its antioxidant potential. Cellular

damage induced by oxidative stress has been implicated in a variety of chronic diseases, such as cancer and neurodegenerative disorders. The antioxidant action of papaya is also very relevant in dermo-cosmetics, as many skincare creams have anti-aging action. The beauty and health of the skin, hair, and nails are directly linked to a diet rich in vitamins and minerals, so this fruit has many benefits at this level. The anti-inflammatory power of papaya is useful in reducing inflammation and oxidation parameters. Its anti-tumor action is also noteworthy.

Given the main nutritional and health applications of fermented papaya described in the literature, this review aimed to emphasize the importance of early daily intake of a very potent antioxidant compound, such as fermented papaya, to possibly eliminate free radicals and control the aging process and prevent the development of various diseases. However, an in-depth investigation based on its pharmacokinetic properties as well as clinical trials is required. Further studies are also needed to know the exact composition of fermented papaya supplements and which compounds are responsible for their actions. In addition, the availability of a huge variety of fermented papaya supplements requires a review of the legal provisions for drug manufacturing. Hence, it is important that the agencies responsible for the supplement's commercialization verify the compliance of fermented papaya supplements. There is already a brand with many in vivo and in vitro studies (FPP®). However, not all brands available on the market can be produced with the same fermentation procedure.

Author Contributions: Conceptualization, M.L., P.C. and T.R.; methodology, M.L. and P.C.; writing—original draft preparation, M.L. and T.R.; writing—review and editing, P.A.G., P.C. and L.B.; supervision, P.A.G., P.C. and L.B.; funding acquisition, P.A.G., P.C. and L.B. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e a Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the project UIDB/50006/2020 is acknowledged L.B. acknowledges funding from FCT through program DL 57/2016-Norma transitória. Financial support was granted to P.C. by the "Support Program for Training and Technical-Scientific Update of Teaching Staff of ESS-P.Porto" (Order ESS/PR-23/2019, Order ESS/PR-5/2020 and Order ESS/P-20/2021.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors gratefully acknowledge the Research Centre on Health and Environment, Department of Pharmacy, School of Allied Health Sciences, Polytechnic Institute of Porto, Porto, Portugal, for providing installations; the University of Salamanca for financial support; and supervisors for helpful suggestions.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bell, V.; Ferrão, J.; Fernandes, T. Nutritional Guidelines and Fermented Food Frameworks. *Foods* **2017**, *6*, 65. [CrossRef] [PubMed]
2. Maicas, S. The Role of Yeasts in Fermentation Processes. *Microorganisms* **2020**, *8*, 1142. [CrossRef] [PubMed]
3. Marco, M.L.; Heeney, D.; Binda, S.; Cifelli, C.J.; Cotter, P.D.; Foligne, B.; Gänzle, M.; Kort, R.; Pasin, G.; Pihlanto, A.; et al. Health benefits of fermented foods: Microbiota and beyond. *Curr. Opin. Biotechnol.* **2017**, *44*, 94–102. [CrossRef] [PubMed]
4. Motarjemi, Y. Impact of small scale fermentation technology on food safety in developing countries. *Int. J. Food Microbiol.* **2002**, *75*, 213–229. [CrossRef]
5. Franz, C.M.; Huch, M.; Mathara, J.M.; Abriouel, H.; Benomar, N.; Reid, G.; Galvez, A.; Holzapfel, W.H. African fermented foods and probiotics. *Int. J. Food Microbiol.* **2014**, *190*, 84–96. [CrossRef]
6. Agyei, D.; Owusu-Kwarteng, J.; Akabanda, F.; Akomea-Frempong, S. Indigenous African fermented dairy products: Processing technology, microbiology and health benefits. *Crit. Rev. Food Sci. Nutr.* **2019**, *60*, 991–1006. [CrossRef]
7. Dimidi, E.; Cox, S.R.; Rossi, M.; Whelan, K. Fermented foods: Definitions and characteristics, impact on the gut microbiota and effects on gastrointestinal health and disease. *Nutrients* **2019**, *11*, 1806. [CrossRef]

8. Somanah, J.; Putteeraj, M.; Aruoma, O.I.; Bahorun, T. Discovering the health promoting potential of fermented papaya preparation—its future perspectives for the dietary management of oxidative stress during diabetes. *Fermentation* **2018**, *4*, 83. [CrossRef]
9. Mackowiak, P.A. Recycling metchnikoff: Probiotics, the intestinal microbiome and the quest for long life. *Front. Public Health* **2013**, *1*, 52. [CrossRef]
10. Sivamaruthi, B.S.; Kesika, P.; Chaiyasut, C. Toxins in fermented foods: Prevalence and preventions—a mini review. *Toxins* **2018**, *11*, 4. [CrossRef]
11. Tsukamoto, Y.; Ichise, H.; Kakuda, H.; Yamaguchi, M. Intake of fermented soybean (natto) increases circulating vitamin K 2 (menaquinone-7) and γ-carboxylated osteocalcin concentration in normal individuals. *J. Bone Miner. Metab.* **2000**, *18*, 216–222. [CrossRef] [PubMed]
12. Tapsell, L.C. Fermented dairy food and CVD risk. *Br. J. Nutr.* **2015**, *113*, S131–S135. [CrossRef] [PubMed]
13. Pinnamaneni, R. Nutritional and medicinal value of papaya (*Carica papaya* Linn.). *World J. Pharm. Pharm. Sci.* **2017**, *6*, 2559–2578. [CrossRef]
14. Vij, T.; Prashar, Y. A review on medicinal properties of *Carica papaya* Linn. *Asian Pac. J. Trop. Dis.* **2015**, *5*, 1–6. [CrossRef]
15. Moy, J.H. Nutrient Composition and Fruit Chemistry. In *Encyclopedia of Food and Health*; Elsevier: Amsterdam, The Netherlands, 2016.
16. Santana, L.F.; Inada, A.C.; Santo, B.L.S.D.E.; Filiú, W.F.O.; Pott, A.; Alves, F.M.; Guimarães, R.D.C.A.; Freitas, K.D.C.; Hiane, P.A. Nutraceutical Potential of *Carica papaya* in Metabolic Syndrome. *Nutrients* **2019**, *11*, 1608. [CrossRef] [PubMed]
17. Sancho, L.E.G.-G.; Yahia, E.; González-Aguilar, G.A. Identification and quantification of phenols, carotenoids, and vitamin C from papaya (*Carica papaya* L., cv. Maradol) fruit determined by HPLC-DAD-MS/MS-ESI. *Food Res. Int.* **2011**, *44*, 1284–1291. [CrossRef]
18. Saeed, F.; Arshad, M.U.; Pasha, I.; Naz, R.; Batool, R.; Khan, A.A.; Nasir, M.A.; Shafique, B. Nutritional and Phyto-Therapeutic Potential of Papaya (*Carica papaya* Linn.): An Overview. *Int. J. Food Prop.* **2014**, *17*, 1637–1653. [CrossRef]
19. Wall, M.M. Ascorbic acid, vitamin A, and mineral composition of banana (*Musa* sp.) and papaya (*Carica papaya*) cultivars grown in Hawaii. *J. Food Compos. Anal.* **2006**, *19*, 434–445. [CrossRef]
20. Kermanshai, R.; McCarry, B.E.; Rosenfeld, J.; Summers, P.S.; Weretilnyk, E.A.; Sorger, G.J. Benzyl isothiocyanate is the chief or sole anthelmintic in papaya seed extracts. *Phytochemistry* **2001**, *57*, 427–435. [CrossRef]
21. De la Cruz, J.; Vela, G.; García, H.S. Pawpaw: Post-Havest Operation, INPhO-Post-Harvest Compendium. Available online: https://www.fao.org/publications/card/en/c/4ffad9a9-c89a-4a7f-8891-cbf294212fd1/ (accessed on 14 January 2021).
22. Williams, D.J.; Pun, S.; Chaliha, M.; Scheelings, P.; O'Hare, T. An unusual combination in papaya (*Carica papaya*): The good (glucosinolates) and the bad (cyanogenic glycosides). *J. Food Compos. Anal.* **2013**, *29*, 82–86. [CrossRef]
23. Singh, S.P.; Kumar, S.; Mathan, S.V.; Tomar, M.S.; Singh, R.K.; Verma, P.K.; Kumar, A.; Kumar, S.; Singh, R.P.; Acharya, A. Therapeutic application of *Carica papaya* leaf extract in the management of human diseases. *DARU J. Pharm. Sci.* **2020**, *28*, 735–744. [CrossRef] [PubMed]
24. Nguyen, T.T.T.; Shaw, P.N.; Parat, M.-O.; Hewavitharana, A.K. Anticancer activity of *Carica papaya*: A review. *Mol. Nutr. Food Res.* **2012**, *57*, 153–164. [CrossRef]
25. Am, A.R.A.F.O.M. Proximate analysis, antioxidant and antiproliferative activities of different parts of *Carica papaya*. *J. Nutr. Food Sci.* **2014**, *04*, 267. [CrossRef]
26. Ayoola, P.B.; Adeyeye, A. Phytochemical and nutrient evaluation of *Carica papaya* (pawpaw) leaves. *Int. J. Recent Res. Appl. Stud.* **2010**, *5*, 325–328.
27. Malacrida, C.R.; Kimura, M.; Jorge, N. Characterization of a high oleic oil extracted from papaya (*Carica papaya* L.) seeds. *Food Sci. Technol.* **2011**, *31*, 929–934. [CrossRef]
28. Length, F. Physicochemical and nutritional qualities of *Carica papaya* seed products. *J. Med. Plants Res.* **2011**, *5*, 3113–3117.
29. Budiarti, M.; Maruzy, A.; Mujahid, R.; Sari, A.N.; Jokopriyambodo, W.; Widayat, T.; Wahyono, S. The use of antimalarial plants as traditional treatment in Papua Island, Indonesia. *Heliyon* **2020**, *6*, e05562. [CrossRef]
30. Julianti, T.; Oufir, M.; Hamburger, M. Quantification of the antiplasmodial alkaloid Carpaine in papaya (*Carica papaya*) leaves. *Planta Med.* **2014**, *80*, 1138–1142. [CrossRef]
31. Kovendan, K.; Murugan, K.; Kumar, A.N.; Vincent, S.; Hwang, J.-S. Bioefficacy of larvicdial and pupicidal properties of *Carica papaya* (Caricaceae) leaf extract and bacterial insecticide, spinosad, against chikungunya vector, Aedes aegypti (Diptera: Culicidae). *Parasitol. Res.* **2011**, *110*, 669–678. [CrossRef]
32. Ashour, A.; Amen, Y.; Nakagawa, T.; Niwa, Y.; Mira, A.; Ohnuki, K.; Murakami, S.; Imao, M.; Shimizu, K. A new aliphatic ester of hydroxysalicylic acid from fermented *Carica papaya* L. preparation with a potential hair growth stimulating activity. *Nat. Prod. Res.* **2018**, *34*, 1750–1755. [CrossRef]
33. Zhang, S.; Hu, C.; Guo, Y.; Wang, X.; Meng, Y. Polyphenols in fermented apple juice: Beneficial effects on human health. *J. Funct. Foods* **2021**, *76*, 104294. [CrossRef]
34. Jiang, H.-Y.; Shii, T.; Matsuo, Y.; Tanaka, T.; Jiang, Z.-H.; Kouno, I. A new catechin oxidation product and polymeric polyphenols of post-fermented tea. *Food Chem.* **2011**, *129*, 830–836. [CrossRef] [PubMed]
35. Fujita, Y.; Tsuno, H.; Nakayama, J. Fermented papaya preparation restores age-related reductions in peripheral blood mononuclear cell cytolytic activity in tube-fed patients. *PLoS ONE* **2017**, *12*, e0169240. [CrossRef] [PubMed]

36. Rimbach, G.; Park, Y.C.; Guo, Q.; Moini, H.; Qureshi, N.; Saliou, C.; Takayama, K.; Virgili, F.; Packer, L. Nitric oxide synthesis and TNF-α secretion in RAW 264.7 macrophages: Mode of action of a fermented papaya preparation. *Life Sci.* **2000**, *67*, 679–694. [CrossRef]
37. Zhang, J.; Mori, A.; Chen, Q.; Zhao, B. Fermented papaya preparation attenuates β-amyloid precursor protein: β-amyloid–mediated copper neurotoxicity in β-amyloid precursor protein and β-amyloid precursor protein Swedish mutation overexpressing SH-SY5Y cells. *Neuroscience* **2006**, *143*, 63–72. [CrossRef]
38. Marotta, F.; Weksler, M.; Naito, Y.; Yoshida, C.; Yoshioka, M.; Marandola, P. Nutraceutical supplementation: Effect of a fermented papaya preparation on redox status and dna damage in healthy elderly individuals and relationship with gstm1 genotype: A randomized, placebo-controlled, cross-over study. *Ann. N. Y. Acad. Sci.* **2006**, *1067*, 400–407. [CrossRef] [PubMed]
39. Marotta, F.; Koike, K.; Lorenzetti, A.; Jain, S.; Signorelli, P.; Metugriachuk, Y.; Mantello, P.; Locorotondo, N. Regulating Redox Balance Gene Expression in Healthy Individuals by Nutraceuticals: A Pilot Study. *Rejuvenation Res.* **2010**, *13*, 175–178. [CrossRef]
40. Hiramoto, K.; Imao, M.; Sato, E.F.; Inoue, M.; Mori, A. Effect of fermented papaya preparation on dermal and intestinal mucosal immunity and allergic inflammations. *J. Sci. Food Agric.* **2008**, *88*, 1151–1157. [CrossRef]
41. You, Z.; Sun, J.; Xie, F.; Chen, Z.; Zhang, S.; Chen, H.; Liu, F.; Li, L.; Chen, G.; Song, Y.; et al. Modulatory Effect of Fermented Papaya Extracts on Mammary Gland Hyperplasia Induced by Estrogen and Progestin in Female Rats. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 1–11. [CrossRef]
42. Yoshino, F.; Lee, M.-C.-I.; Kobayashi, K.; Hayashi, Y.; Aruoma, O.I. Assessment of the effect of fermented papaya preparation on oxidative damage in spontaneously hypertensive rat brain using electron spin resonance (ESR) imaging and L-band ESR spectroscopy. *J. Funct. Foods* **2009**, *1*, 375–380. [CrossRef]
43. Murakami, S.; Eikawa, S.; Kaya, S.; Imao, M.; Aji, T. Anti-tumor and immunoregulatory effects of fermented papaya preparation (FPP: SAIDO-PS501). *Asian Pac. J. Cancer Prev.* **2016**, *17*, 3077–3084.
44. Logozzi, M.; Mizzoni, D.; Di Raimo, R.; Macchia, D.; Spada, M.; Fais, S. Oral Administration of fermented papaya (FPP®) controls the growth of a murine melanoma through the in vivo induction of a natural antioxidant response. *Cancers* **2019**, *11*, 118. [CrossRef] [PubMed]
45. Logozzi, M.; Di Raimo, R.; Mizzoni, D.; Andreotti, M.; Spada, M.; Macchia, D.; Fais, S. Beneficial effects of fermented papaya preparation (FPP®) supplementation on redox balance and aging in a mouse model. *Antioxidants* **2020**, *9*, 144. [CrossRef] [PubMed]
46. Marotta, F.; Celep, G.S.; Cabeca, A.; Polimeni, A. Novel concepts on functional foods and nutrigenomics in healthy aging and chronic diseases: A review of fermented papaya preparation research progress. *Funct. Foods Health Dis.* **2012**, *2*, 120. [CrossRef]
47. Khan, I.; Shaikh, H. Cooley Anemia. Available online: https://www.ncbi.nlm.nih.gov/books/NBK557522/ (accessed on 10 January 2021).
48. Cotoraci, C.; Ciceu, A.; Sasu, A.; Hermenean, A. Natural Antioxidants in Anemia Treatment. *Int. J. Mol. Sci.* **2021**, *22*, 1883. [CrossRef] [PubMed]
49. Amer, J.; Goldfarb, A.; Rachmilewitz, E.A.; Fibach, E. Fermented papaya preparation as redox regulator in blood cells ofβ-thalassemic mice and patients. *Phytother. Res.* **2008**, *22*, 820–828. [CrossRef] [PubMed]
50. Fibach, E.; Tan, E.-S.; Jamuar, S.; Ng, I.; Amer, J.; Rachmilewitz, E.A. Amelioration of oxidative stress in red blood cells from patients with β-thalassemia major and intermedia and E-β-thalassemia following administration of a fermented papaya preparation. *Phytother. Res.* **2010**, *24*, 1334–1338. [CrossRef]
51. Ghoti, H.; Rosenbaum, H.; Fibach, E.; Rachmilewitz, E.A. Decreased hemolysis following administration of antioxidant—fermented papaya preparation (FPP) to a patient with PNH. *Ann. Hematol.* **2010**, *89*, 429–430. [CrossRef]
52. Ghoti, H.; Fibach, E.; Dana, M.; Abu Shaban, M.; Jeadi, H.; Braester, A.; Matas, Z.; Rachmilewitz, E. Oxidative stress contributes to hemolysis in patients with hereditary spherocytosis and can be ameliorated by fermented papaya preparation. *Ann. Hematol.* **2010**, *90*, 509–513. [CrossRef]
53. Maritim, A.C.; Sanders, R.A.; Watkins, J.B., 3rd. Diabetes, oxidative stress, and antioxidants: A review. *J. Biochem. Mol. Toxicol.* **2003**, *17*, 24–38. [CrossRef]
54. Danese, C.; Esposito, D.; D'Alfonso, V.; Cirene, M.; Ambrosino, M.; Colotto, M. Plasma glucose level decreases as collateral effect of fermented papaya preparation use. *Clin. Ter.* **2006**, *157*, 195–198. [PubMed]
55. Collard, E.; Roy, S. Improved function of diabetic wound-site macrophages and accelerated wound closure in response to oral supplementation of a fermented papaya preparation. *Antioxid. Redox Signal.* **2010**, *13*, 599–606. [CrossRef] [PubMed]
56. Van Der Schaft, N.; Schoufour, J.D.; Nano, J.; Jong, J.C.K.-D.; Muka, T.; Sijbrands, E.J.G.; Ikram, M.A.; Franco, O.H.; Voortman, T. Dietary antioxidant capacity and risk of type 2 diabetes mellitus, prediabetes and insulin resistance: The Rotterdam Study. *Eur. J. Epidemiol.* **2019**, *34*, 853–861. [CrossRef] [PubMed]
57. Sluijs, I.; Cadier, E.; Beulens, J.W.J.; Spijkerman, A.M.W.; van der Schouw, Y.T. Dietary intake of carotenoids and risk of type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* **2015**, *25*, 376–381. [CrossRef]
58. Roohbakhsh, A.; Karimi, G.; Iranshahi, M. Carotenoids in the treatment of diabetes mellitus and its complications: A mechanistic review. *Biomed. Pharmacother.* **2017**, *91*, 31–42. [CrossRef] [PubMed]
59. Mikhal, E.V.; Ivanova, A.V.; Anurov, M.V.; Titkova, S.M.; Penkov, L.Y.; Kharaeva, Z.F.; Korkina, L.G. Wound-Healing Effect of Papaya-Based Preparation in Experimental Thermal Trauma. *Bull. Exp. Biol. Med.* **2004**, *6*, 560–562. [CrossRef] [PubMed]

60. Bertuccelli, G.; Zerbinati, N.; Marcellino, M.; Kumar, N.S.N.; He, F.; Tsepakolenko, V.; Cervi, J.; Lorenzetti, A.; Marotta, F. Effect of a quality-controlled fermented nutraceutical on skin aging markers: An antioxidant-control, double-blind study. *Exp. Ther. Med.* **2016**, *11*, 909–916. [CrossRef] [PubMed]
61. Shi, L.; Ermis, R.; Lam, K.; Cowart, J.; Attar, P.; Aust, D. Study on the debridement efficacy of formulated enzymatic wound debriding agents by in vitro assessment using artificial wound eschar and by an in vivo pig model. *Wound Repair Regen.* **2009**, *17*, 853–862. [CrossRef] [PubMed]