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Anti-Inflammatory and Anti-Oxidant effects of *Manilkara zapota* and *Hylocereus undantus*: A Complete Review

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Abstract

This article summarises recent scientific results regarding the anti-inflammatory and antioxidant activities of the phytochemical elements in *Manilkara zapota* (i.e,Sapodilla) and *Hylocereus undatus* (i.e, Dragon fruit). The Central American native sapodilla has strong antioxidant properties thanks to its rich composition of bioactive substances, which includes polyphenols and vitamins. Sapodilla may be a contender for treating inflammatory ailments like arthritis and gastrointestinal issues. According to recent studies, it has anti-inflammatory properties. Another tropical treasure bursting with antioxidants is *Hylocereus undatus*, also referred to as dragon fruit. Its beautiful pink flesh is packed with betalains, polyphenols, and significant amounts of vitamin C, all of which add to its strong antioxidant capacity. Additionally, by blocking inflammatory cytokines and enzymes, dragon fruit has demonstrated promise in reducing inflammation.

Key words: Manilkara zapota, Hylocereus undantus, Sapota, Dragon fruit, Anti-Inflammatory effects, Anti-oxidant effects.

Introduction

The extent, diversity, distinctiveness, and intricacy of plant biodiversity on a global scale, along with their significant therapeutic potentials, have been under investigation for a considerable duration. From the beginning of the world for many centuries, plants have been source of wide variety of biologically active compounds and used extensively as as pure compounds for treating numerous disease conditions. Plants have evolved a remarkable ability to synthesize a multitude of bioactive compounds that possess significant anti-inflammatory and antioxidant properties. The diverse range of compounds found in plants, including flavonoids, polyphenols, and vitamins, among others, contribute their valuable properties by balancing the immune response and minimizing inflammatory mechanisms[1,2].

An extensive variety of plants famous for their excellent anti-inflammatory and antioxidant qualities have drawn the keen interest of scientific explorers. Many plant-derived compounds, such as flavonoids, terpenoids, and alkaloids, have been shown to possess anti-inflammatory effects. These compounds often target key

inflammatory pathways, modulating the release of pro-inflammatory molecules and reducing the overall inflammatory response. By inhibiting enzymes like cyclooxygenase (COX) and lipoxygenase (LOX), which are involved in the synthesis of inflammatory mediators, these compounds help maintain a balanced immune response and mitigate excessive inflammation. Plants are rich sources of antioxidants like vitamins (e.g., vitamin C and E), polyphenols (e.g., resveratrol and quercetin), and carotenoids (e.g., beta-carotene and lycopene). These compounds neutralize ROS and protect cells from oxidative damage by donating electrons and breaking the chain reaction of free radical formation. Furthermore, some plant antioxidants can enhance the body's endogenous antioxidant defense systems, reinforcing the body's ability to combat oxidative stress.
Likewise, the intriguing characteristics of Sapodilla and Dragon Fruit are highlighted in this context. They are widely consumed for their astonishing properties and several health benefits.

Manilkara zapota is one of the tropical plants belonging to the Sapotacea family. Sapota contains abundance of vital nutrients that promotes general health and well-being. (Antala et al., 2021). The nutrient-rich fruit includes glucose, fructose, sucrose, dietary fiber, minerals (calcium, iron, phosphorus, potassium, and magnesium), vitamins (vitamin A, vitamin C, thiamine, riboflavin, pantothenic acid, and folate), as well as a number of phytochemicals, fatty acids, and polyamines[3]. With a rich reservoir of antioxidants, polyphenols, and other bioactive compounds, Sapodilla natural counteracts against oxidative stress and inflammation[4]. Furthermore, it also has plenty of additional actions such as hey have a variety of pharmaceutical properties like antimicrobial, anti-inflammatory, antipyretic, antiviral, antidiarrheal, anti-hyperglycemic, anti-parasitic, antibiotics, anticancer, antitumor, and hyper-cholesteraemic properties[4].

Hylocereus undatus is also known as Dragon Fruit and Pitaya belonging to family Cactaceae. There are three types of dragon fruit: *Hylocereus undatus*, pink skin with white flesh; *Hylocereus polyrhizus, Hylocereus costaricencis and Hylocereus megalanthus*[5]. *Hylocereus undatus* boasts a wealth of nutrients and minerals, including but not limited to vitamin B1, vitamin B2, vitamin B3, and vitamin C, as well as protein, fat, carbohydrate, crude fiber, flavonoid, thiamin, niacin, pyridoxine, kobalamin, glucose, phenolic compounds, betacyanins, polyphenols, carotene, phosphorus, iron, and phytoalbumin6. Particularly noteworthy is its abundance of phytoalbumins, highly prized for their potent antioxidant properties6. Utilized for various health benefits, the fruit is employed for its hypocholesterolemic, antimicrobial, and antioxidant properties, making it effective in addressing constipation. Additionally, it is recognized for its anti-cancer properties, immune system-boosting qualities, usefulness in diabetes management, cholesterol level maintenance, promotion of healthy hair and skin, prevention of anemia, enhancement of appetite, and support for vision and brain function[7].

Botanical Background and Taxonomy

	Manilkara zapota[4]	**Hylocereus undatus[5]**
Domain	Eukaryota	Eukaryota
Kingdom	Plantae	Plantae
Phylum	Spermatophyta	Magnoliophyta
Class	Dicotyledonae	Magnoliopsida
Order	Ebenales	Caryophyllales
Family	Sapotaceae	Cactaceae
Subfamily	Sapotoideae	Cactoideae
Genus	Manilkara	Hylocereus
Species	Manilkara zapota	Hylocereus undatus

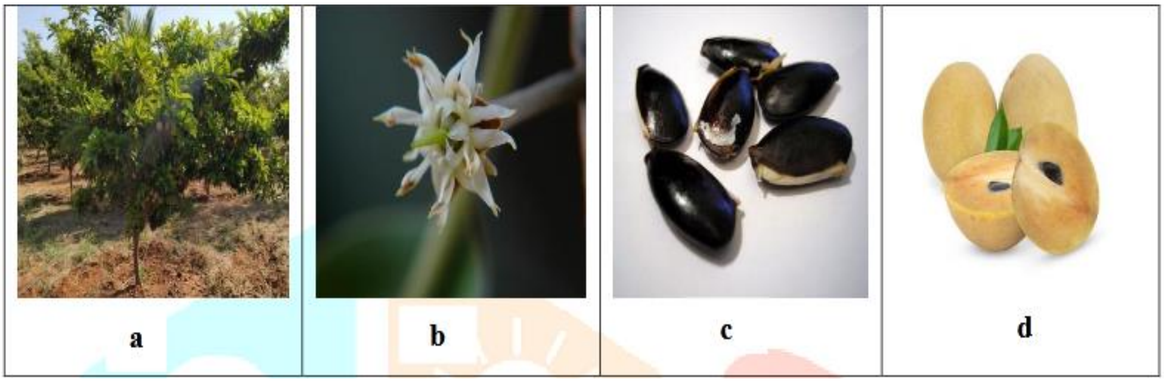

Figure 1[4]. Sapota (*Manilkara zapota*): (a) whole plant; (b) flower; (c) seeds; (d) fruit.

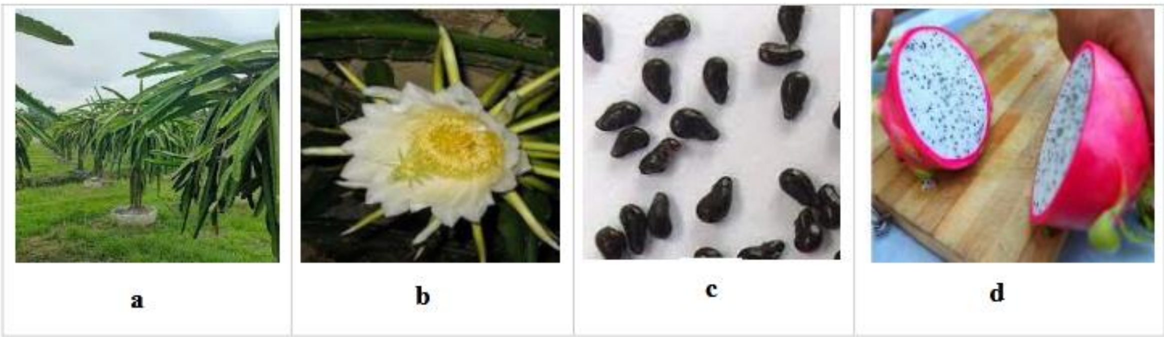

Figure 2[7]. Pitaya (*Hylocereus undatus*): (a) whole plant; (b) flower; (c) seeds; (d) fruit.

Phytochemical Composition

Phytochemicals are substances identified in plants that have the potential to positively impact human metabolism, presenting advantages for averting chronic and degenerative illnesses[8]. According to their roles in plant metabolism, phytoconstituents are essentially split into two classes, similar to primary and secondary metabolites. The primary metabolites include simple sugars, amino acids, proteins, and chlorophyll, whereas secondary metabolites include alkaloids, terpenoids, flavonoids, tannins, and others[8].

Manilkara zapota: is reported to contain phenolic compounds such as: Myricetin-3-O-α-L-rhaminopyranoside, Apigenin-7-O-α-L-rhamnopyranoside and Caffeic acid, which isolated from leaves, Quercetrin, (+)-catechin, (-)-epicatechin, (+)-gallocatechin, Gallic acid, dihydromyricetin, Methylchlorogenate, Methyl-4-O-galloyl chlorogenate, 4-O- galloylchlorogenic acid which isolated from fruits. D-quercitol was reported in seeds and leaves. Three phenolic compounds isolated from the fruits of *Manilkara zapota*; Leucodelphinidine, Leucocyanidine, Leucoperalgonidine[9,10].

The phytochemical constituents present in dragon fruit majorly belong to class of phenols, sterols, flavonoids, fatty acids, and tocopherol. Phytoconstituents extracted from species of pitaya, namely, H. undatus and H. polyrhizus, include n-hexadecanoic acid, 1-hexadecyne, (Z, Z)-9, 12-octadecadienoic acid, 2-chloroethyl linoleate, oleic acid, octacosane , 17-pentatriacontene, trichloroacetic acid, hexadecyl ester, 1-nonadecene, 6-tetradecanesulfonic acid, butyl ester, 1,2-benzenedicarboxylic acid, mono (2-ethylhexyl) ester, phthalic acid, 6-ethyloct-3-yl 2-ethylhexyl ester, eicosane, tetratriacontane, 1-tetracosanol, heptacosane, campesterol, stigmasterol, squalene, 11-hexacosyne, octadecanal, nonacosane, octadecane, γ-sitosterol, α-amyrin, hexadecyl oxirane, β-amyrin, ergosta-4,6,8(14),22-tetraen-3-one, docosane, stigmast-4-en-3-one, β-sitosterol[11,12].

Anti-Inflammatory Activity

When higher organisms are exposed to harmful assaults like microbial infection, tissue damage, or other toxic situations, they develop inflammation as a protective tactic. Inflammation is a defense mechanism following a tissue injury, trauma, infection and other noxious condition. It is a crucial immunological response by the host that promotes the elimination of toxic stimuli as well as the healing of damaged tissue[13].

In response to injury, infection, foreign invaders or any irritant (external or internal), inflammation is usually initiated within minutes[14]. At the tissue level, inflammation is characterized by five cardinal signs. They are redness, swelling, heat, pain, and loss of tissue function, which result from local immune, vascular and inflammatory cell responses to infection or injury[2]. As innate immune system is the major contributor to inflammation, immune cells such as macrophages, dendritic cells, mast cells, neutrophils and lymphocytes play important roles in inflammatory responses. Since innate immunity serves as the first line of defence for the host against outside intruders and dangerous chemicals, acute inflammation has been viewed as a component of this system[15].

Acute inflammation is associated with increased vascular permeability, capillary infiltration and emigration of leukocytes[2]. Typically, in instances of acute inflammatory responses, cellular and molecular events and interactions adeptly work together to minimize potential harm or infection. Irrespective of the severity and dependency of the detrimental insult, the mechanism of inflammation is as follows; Cell surface pattern receptors recognizes the detrimental stimuli, inflammatory pathways are activated, inflammatory markers are released and inflammatory cells are recruited. This corrective process plays a role in restoring tissue balance and resolving acute inflammation. Nevertheless, if acute inflammation goes unchecked, it can evolve into a chronic state, contributing to the development of various chronic inflammatory diseases[16]. Chronic inflammation is associated with infiltration of mononuclear immune cells, macrophages, monocytes, neutrophils, fibroblast activation, proliferation (angiogenesis) and fibrosis and inflammatory mediator release[17].

The anti-inflammatory effects of *Manilkara zapota* (Sapodilla) have been researched for quite a while now. Sapodilla or sapota possesses a diverse array of bioactive compounds that exhibit the potential to mitigate inflammation, a key contributor to various chronic diseases. One of the primary components responsible for the anti-inflammatory properties of *M. zapota* is its polyphenolic content. Polyphenols are plant-derived compounds known for their antioxidant and anti-inflammatory effects. Research has shown that M. zapota contains significant levels of various polyphenols, including flavonoids and tannins. These compounds have been found to exert anti-inflammatory effects by inhibiting the activity of enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), which are involved in the synthesis of inflammatory mediators. A particular flavonoid present in *M. zapota*, quercetin, has been linked to potent anti-inflammatory effects. Quercetin is known for its ability to modulate immune responses and inhibit the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). These cytokines play a crucial role in promoting and sustaining the inflammatory process. By suppressing their release, quercetin helps regulate the immune system and dampen excessive inflammation[18,19]. Furthermore, M. zapota extracts have been shown in laboratory experiments to reduce the levels of inflammatory markers. These markers include C-reactive protein (CRP) and prostaglandins, which are linked to inflammatory reactions. By lowering the levels of these markers, M. zapota demonstrates its ability to reduce systemic inflammation, which is a frequent underlying cause in chronic diseases such as cardiovascular disorders and metabolic syndrome. M. zapota's antioxidant qualities also contribute greatly to its anti-inflammatory properties.

In a study conducted by Ganguly et al[20], it was found that the ethanolic leaf extract of chicozapote demonstrated time-dependent anti-inflammatory activity. The efficacy of the extract surpassed that of the standard drug, diclofenac sodium (100 mg/kg), with a 92.75% inhibition after reaching its peak at 6 hours. The extract's impact was particularly notable in the second phase, confirming its action mechanism as a prostaglandin (PG) reducing agent that inhibits the synthesis of enzymes in the cyclooxygenase pathway produced during inflammatory responses. Similarly, Konuku et al[21] proposed that the anti-inflammatory effect of the ethyl acetate leaf extract is attributed to the inhibition of inflammatory enzymes, specifically cyclooxygenase-2, 5-lipoxygenase, and phospholipase-2 (COX-2, 5-LOX, and PLA-2). This effect is likely due to the presence of QE in the extracts, which was used as a standard drug for 5-LOX inhibition (IC50 = 4.851 μg/ml), and the action mechanisms have been elucidated. QE is known to negatively regulate lipopolysaccharide-induced toll-like receptor 4 (TLR4) expression and signaling, preventing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) translocation and the activation of the Nrf2 signaling cascade. It also inhibits COX-2 and inducible nitric oxide synthase (iNOS) expression, reducing pro-inflammatory cytokine production by suppressing extracellular signal-regulated kinase (ERK) activation and p38 mitogen-activated protein (MAP) kinase22. Hossain et al23 concluded, through histamine-induced paw edema, that chicozapote methanolic bark extract exhibits antihistamine activity with a dose-dependent behavior. This suggests that the mechanism is mediated through the inhibition of inflammatory mediators and can be attributed to a high flavonoid content, particularly QE. GA is also a dominant compound in chicozapote, and its anti-inflammatory response is suggested to interfere with polymorphonuclear leukocyte function. Liu et al[24] reported anti-inflammatory effects of a 90% ethanolic fruit extract from chicozapote. The results showed a significant decrease in nitric oxide (NO) production, observed in mouse macrophage RAW 264.7 cells (IC50 = 7.65 ± 0.12 μg/ml). The anti-inflammatory potential of AG, identified in the chicozapote phytochemical profile, was evaluated. Cells treated with this compound exhibited reduced production of PG in a dose-dependent manner, similar to other chicozapote extracts, and the anti-inflammatory mechanism primarily involves the inhibition of PGE2 synthesis[25,26]. Due to its richness in catechins, known to ameliorate cholinergic dysfunction by regulating acetylcholine (ACh) content and acetylcholinesterase (AChE) activity in hippocampal tissues, chicozapote may suppress the expression of NF-κB and inhibit the synthesis of pro-inflammatory cytokines[27,28].

The anti-inflammatory effects of H. undatus lies in the flavonoids, polyphenolic compounds with diverse physiological effects. Notably, quercetin and kaempferol emerge as key players, engaging in a complex dance with inflammatory pathways. By inhibiting enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), these flavonoids disrupt the production of inflammatory molecules, curbing the escalation of inflammation at its source. Distinctive pigments known as betalains infuse Dragon Fruit with its vibrant hues and potent antioxidative capacity. These compounds actively neutralize free radicals, unstable molecules that trigger oxidative stress and fuel inflammation. Additionally, betalains exert influence at the molecular level by modulating transcription factors like nuclear factor-kappa B (NF-κB), which orchestrate the expression of genes involved in inflammation. This dual role of betalains in both antioxidative defense and molecular regulation underlines their significance in Dragon Fruit's anti-inflammatory effects. Further enriching Dragon Fruit's profile are compounds that regulate cytokine release, thus shaping immune responses. By modulating the production of cytokines, Dragon Fruit contributes to immune harmony, preventing the runaway immune responses that characterize chronic inflammation and autoimmune conditions. This intricate immunomodulatory role complements the fruit's anti-inflammatory actions, fostering a balanced immune environment[29].

Anthocyanins (cyanidin-3-glucoside, delphinidin-3-glucoside, and pelargonidin-3-glucoside) were discovered by Saenjum et al[30,31], in pitaya red flesh and peel. In vitro, the pulp was richer in the first anthocyanin (cyanidin-3-glucoside), reduced the formation of reactive oxygen and nitrogen species, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), cytotoxicity. Another study found that an extract of dragon fruit pulp and peel, as well as extracted squalene, suppressed pro-inflammatory enzymes such as cyclooxygenase-2-lipoxygenase and acetylcholinesterase, implying that this fruit has the capacity to control and control inflammatory processes. Different mechanisms, such as prostaglandins, leukotrienes, and cholinergic pathways may be involved[32]. Amim et al[33] discovered that the extracts of H. polyrhizus and H. undatus had different effects (anti-inflammatory, antioxidant, and anti-bacterial properties) (the aqueous extract of H. polyrhizus showed more significant effects than H. undatus). When compared to the ethyl acetate and ethanolic extracts, the investigators discovered that the aqueous extract of these species resulted in better protective anti-inflammatory and antioxidant effects. Using H. polyrhizus, Al-Radadi et al[34] discovered strong anti-inflammatory, anti-diabetic, anti-Alzheimer, and cytotoxic properties of gold nanoparticles.

Antioxidant Activity

As part of routine metabolic functions, the cells of human body generates free radicals. To counteract these free radicals, cells also create antioxidants. Antioxidants and free radicals can generally coexist in harmony within the body. An imbalance between the production of free radicals and reactive metabolites and their elimination by protective mechanisms referred to as antioxidants leads to a term called Oxidative stress[35,36]. This imbalance leads to damage of important biomolecules and cells, with potential impact on the whole organism[37]**.** Although the cell possesses an antioxidant defense system to combat oxidative damage caused by reactive oxygen species (ROS), such damage accrues over the life cycle and has been associated with diseases, aging, and age-related conditions like cardiovascular disease, cancer, neurodegenerative disorders, and various chronic ailments[37].

Naturally, the human body has circulation of variety of nutrients for their antioxidant properties and manufactures antioxidant enzymes to control these destructive chain reactions. For example, vitamin C, vitamin E, carotenes, and lipoic acid. Similarly, plants and animals maintain complex systems of multiple types of antioxidants such as glutathione (GSH), vitamin C, and vitamin E as well as enzymes such as catalase (CAT), superoxide dismutase (SOD), and various peroxidases. Low levels of antioxidants, or inhibition of antioxidant enzymes, causes oxidative stress and damages or kill cells [38,39].

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms, is critical in initiating inflammation. M. zapota contains antioxidants such as vitamin C, vitamin E, and different polyphenols that help neutralise ROS and prevent oxidative damage.

Antioxidants are the chemical compounds that act on oxidation chain reactions by inhibiting or delaying the oxidation of other molecules. Antioxidants protect the human body from harmful effects of free radicals and ROS[40]. Almost all the medicinal plants contain several antioxidants such as carotenoids, flavonoids (flavones, isoflavones, flavonones, anthocyanins), polyphenols (ellagic acid, gallic acid, tannins), saponins, enzymes, vitamins (A, C, E, K) and minerals (copper, manganese, zinc, chromium, iodine, etc)[40]. Natural antioxidants are safer than synthesized antioxidants and they show anti-viral, anti-inflammatory, anti-cancer, anti-mutagenic, anti-tumour and hepatoprotective properties [21].These natural antioxidants are produced in all or any part of plants but mostly leaves are considered as the main source for their synthesis[41,42].

Fruits are recognized for their abundant content of antioxidants, commonly employed to address oxidative stress. The underlying reason for the health-promoting attribute of fruits lies in the extensive array of nutraceutical phytochemicals they contain, including polyphenols, carotenoids, sterols, saponins, terpenes, and vitamins. Certain phytochemical constituents such as phenolics, ascorbic acid, and carotenoids may exert a direct influence on radical-scavenging capabilities. The ability of most of these phytochemicals to alleviate oxidative stress is attributed to their radical-scavenging potential. Continuously growing demand for promising

dietary antioxidant sources because of public awareness has triggered the search for newer, economical, nutritional and multifunctional sources possessing free radical- scavenging potential[43].
Methanolic extracts of sapodilla fruit yielded two antioxidants: Methyl 4-O-galloylchlorogenate and 4-O-galloylchlorogenic acid. Additionally, eight other recognized polyphenolic antioxidants were detected, including methyl chlorogenate, dihydromyricitin, quercitrin, myricitrin, (+) catechin, (-) epicatechin, (+) gallocatechin, and gallic acid**.** Catechin also present in teas is a well-known antioxidant. Natural antioxidants can assist in the protection of human cells against the effects of free radicals that may contribute to cancer forming cells among other diseases[44].
The free radical scavenging abilities of both the pulp and peel of *Manilkara zapota* (sapota) were tested against 2,2-diphenyl-1-picryl hydrazyl (DPPH), 2,2-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS+). The DPPH scavenging activity was evaluated using a slightly modified Brand-Williams spectrophotometric technique. Antioxidants scavenge the 1,1- diphenyl-2-picryl-hydrazyl radical by donating protons, resulting in decreased DPPH. Depending on how many electrons are picked up, the solution loses colour. The decrease in absorbance at 517 nm measures the colour change from purple to yellow after reduction. Methanol was used to dissolve sapota extracts. A freshly manufactured DPPH in methanol (0.2 mM) solution was prepared. 3 mL of this solution was mixed with 1 mL of each of the concentration-varying samples. (100 to 1000 μg/ml). The solution in the test tubes was thoroughly mixed before being incubated in the dark for 30 minutes at room temperature, and absorbance was measured at 517 nm. Instead of extract, the control used an identical volume of DPPH in methanol. As a control, 5 ml of methanol was used. The percentage suppression of radicals due to the extract's antioxidant property was estimated using the formula[45,46]: % inhibition = [(Acontrol - A sample)/Acontrol]* 100.
The ABTS assay works by inhibiting the absorbance of the ABTS radical cation, which has a distinctive long wavelength absorption spectrum. The experiment was carried out using a slightly modified procedure developed by Re et al. (1999). The ABTS radical was created by mixing an ABTS solution (7 mM) with ammonium per sulphate (2.45 mM) and allowing the mixture to remain in the dark for 12 to 16 hours at room temperature. At 745 nm, absorbance was measured. The initial absorption was approximately 2.99. This stock solution was diluted with methanol to a final absorbance value of about 0.7 (0.2) and equilibrated at 30 degrees Celsius. By dissolving the extracts in water, different concentrations of the sample (100 to 1000 g/ml) were obtained. In a microcuvette, 0.3 ml of the material was combined with 3 ml of ABTS working standard. After mixing the solution for 1 minute intervals up to 6 minutes, the absorbance was measured. The total absorbance was calculated. As a control, a working solution of ABTS and 0.3 mL of methanol was utilised. As a control, 3 mL of methanol was used.
The percentage inhibition was calculated according to the formula[45,46]: % inhibition = [(Acontrol - A sample)/Acontrol]* 100.
Hylocereus polyrhizus is rich in betalains and other bioactive compounds such as vitamins and phenolic compounds that exert relevant antioxidant properties and, for these reasons, are related to the prevention of several human diseases. The oil results from the seeds, and the peel is also an essential source of antioxidant compounds. The peel of H. undatus possesses more flavonoids than the flesh[47,48,49]. The antioxidant properties of dragon fruit extract were investigated. Total antioxidant status was reduced in pre-diabetic and normocholesterolemic subjects that consumed red pitaya. Harahap and Amelia[50] showed that fruit extract could minimize oxidative damage production in animals submitted to physical exercises. Other authors have shown that the pulp extract can decrease oxidative damage in STZ-induced diabetes in rats[51]. Putri et al[52], showed that the intake of red dragon fruit could reduce malondialdehyde levels in diabetic rats and, for these reasons, is associated with reducing the oxidative stress related to this disease.

Conclusion

However, while the current research provides insight into its anti-inflammatory effects, further studies are needed to unravel the precise mechanisms of action and establish optimal consumption patterns for harnessing its potential benefits against chronic inflammation and related diseases. Through this exploration, the fruit's promise as a holistic agent for promoting overall wellness and addressing inflammation-related health challenges becomes increasingly apparent.

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