

# CUSTARD APPLE (*Annona squamosa* L.): EXPLORING ITS HEALTH BENEFITS AND MEDICINAL PROPERTIES

## ABSTRACT

Custard apple (*Annona squamosa* L.), a tropical fruit known for its sweet and creamy pulp, has been traditionally valued not only for its taste but also for its health benefits and medicinal properties. Rich in vitamins, minerals, and antioxidants, custard apple plays a significant role in enhancing immune function, improving digestion, and promoting cardiovascular health. The fruit exhibits potent anti-inflammatory, antidiabetic, and anticancer properties, largely attributed to its bioactive compounds such as acetogenins, flavonoids, and alkaloids. Additionally, it has been used in traditional medicine to treat conditions like dysentery, diarrhea, and respiratory issues. This review explores the nutritional profile, phytochemical composition, and therapeutic potential of custard apple, highlighting its role in modern healthcare and its potential for further research in pharmacology and nutraceuticals.

**Keywords:** Custard apple, *Annona squamosa*, health benefits, medicinal properties, antioxidants, acetogenins, traditional medicine etc.

## INTRODUCTION

Custard apple, scientifically known as *Annona squamosa* L., is a tropical fruit belonging to the Annonaceae family. Native to the Caribbean, Central America, and northern South America, this fruit has gained global recognition not only for its sweet, creamy pulp but also for its numerous health benefits and medicinal properties. Custard apple is commonly known by various names across different regions, such as sugar apple, sweetsop, and sitaphal in India. Its unique flavor and texture, combined with its rich nutrient profile, have made it a popular fruit in many parts of the world (Kalidindi *et al.* 2015).

## Nutritional Profile

Custard apple is a powerhouse of essential nutrients, including vitamins, minerals, and antioxidants. It is particularly rich in vitamin C, a potent antioxidant that plays a crucial role in boosting the immune system, combating free radicals, and promoting skin health. The fruit also contains significant amounts of dietary fiber, which aids in digestion and helps prevent constipation. Additionally, custard apple is a good source of vitamins B6 and B12, which are vital for brain health and the synthesis of neurotransmitters (Anaya-Esparza *et al.* 2020). The

mineral content of custard apple is also noteworthy, with high levels of potassium, magnesium, and calcium, all of which are essential for maintaining heart health, bone density, and muscle function. Moreover, the fruit contains beneficial compounds such as polyphenols, flavonoids, and carotenoids, which contribute to its antioxidant and anti-inflammatory properties (El-Chaghaby *et al.* 2014).

### **Health Benefits of Custard Apple**

**Antioxidant Properties:** Custard apple is rich in antioxidants, which help protect the body against oxidative stress and reduce the risk of chronic diseases such as cancer and heart disease. The presence of vitamin C and polyphenolic compounds enhances the fruit's ability to neutralize free radicals and prevent cellular damage (Sundaramahalingam *et al.* 2021).

**Anti-Inflammatory Effects:** Chronic inflammation is a major contributor to various health conditions, including arthritis, cardiovascular diseases, and diabetes. Custard apple's anti-inflammatory properties, attributed to its high content of flavonoids and other bioactive compounds, can help reduce inflammation and alleviate symptoms associated with these conditions (Zahid *et al.* 2018).

**Cardiovascular Health:** The potassium and magnesium in custard apple play a vital role in maintaining cardiovascular health. Potassium helps regulate blood pressure by counteracting the effects of sodium, while magnesium supports heart function and reduces the risk of heart attacks and strokes. Additionally, the fruit's fiber content helps lower cholesterol levels, further promoting heart health (Kumar *et al.* 2019).

**Digestive Health:** Custard apple is an excellent source of dietary fiber, which aids in digestion by promoting regular bowel movements and preventing constipation. The fiber also supports a healthy gut microbiome, which is essential for overall digestive health and the prevention of gastrointestinal disorders (Kumar *et al.* 2019).

**Diabetes Management:** The low glycemic index of custard apple makes it a suitable fruit for individuals with diabetes. It helps regulate blood sugar levels by slowing down the absorption of sugar in the bloodstream. Furthermore, the fruit's high fiber content contributes to better glycemic control and reduces the risk of developing type 2 diabetes (Punia *et al.* 2021).

**Immune System Support:** Vitamin C, one of the primary nutrients in custard apple, is known for its immune-boosting properties. Regular consumption of the fruit can help strengthen the immune system, making the body more resilient to infections and illnesses (Kumar *et al.* 2020).

**Cancer Prevention:** Custard apple contains various bioactive compounds with potential anticancer properties. Studies have shown that the fruit's antioxidants can inhibit the growth of cancer cells and induce apoptosis (programmed cell death) in certain types of cancer. While more research is needed to fully understand these effects, the fruit shows promise as a natural cancer-preventive agent (Kumar *et al.* 2020).

**Skin and Hair Health:** The high levels of vitamin C and antioxidants in custard apple contribute to healthy skin and hair. Vitamin C promotes collagen production, which is essential for maintaining skin elasticity and preventing wrinkles. The antioxidants also protect the skin from damage caused by UV radiation and environmental pollutants (Nishad *et al.* 2021).

### **Medicinal Properties**

The medicinal properties of custard apple extend beyond its nutritional benefits. Traditional medicine systems, such as Ayurveda and Traditional Chinese Medicine (TCM), have long recognized the therapeutic potential of various parts of the custard apple plant, including its leaves, seeds, bark, and roots (Kumar *et al.* 2021).

**Antimicrobial Activity:** Custard apple has been shown to possess antimicrobial properties, making it effective against a range of bacterial and fungal infections. The leaves and seeds, in particular, contain compounds that inhibit the growth of harmful microorganisms, thereby protecting the body from infections (Kumar *et al.* 2021).

**Analgesic and Anti-inflammatory Properties:** The leaves of the custard apple tree have been used traditionally to treat pain and inflammation. Research indicates that these properties are due to the presence of alkaloids and other bioactive compounds that modulate pain pathways and reduce inflammation (Kumar *et al.* 2021).

**Anti-diarrheal Effects:** In traditional medicine, custard apple has been used as a natural remedy for diarrhea. The fruit's astringent properties help reduce intestinal motility and water loss, thereby alleviating diarrhea symptoms (Punia *et al.* 2021).

**Wound Healing:** Custard apple leaves and bark are often used in poultices and topical treatments to promote wound healing. The plant's antimicrobial and anti-inflammatory properties help prevent infections and accelerate the healing process (Al-Nemari *et al.* 2020).

**Neuroprotective Effects:** Emerging research suggests that custard apple may have neuroprotective properties, which could be beneficial in the prevention and management of neurodegenerative diseases such as Alzheimer's and Parkinson's. The antioxidants and

bioactive compounds in the fruit help protect neurons from oxidative stress and inflammation (Mannino *et al.* 2020).

Custard apple (*Annona squamosa* L.) is a fruit that offers a wide range of health benefits and medicinal properties. Its rich nutrient profile, coupled with its antioxidant, anti-inflammatory, and antimicrobial activities, makes it a valuable addition to the diet. Moreover, its potential therapeutic applications in traditional medicine highlight the need for further research to explore and validate these medicinal properties. As scientific interest in custard apple continues to grow, it is likely that this tropical fruit will gain even more recognition for its contributions to health and well-being (Hosseinabadi, 2021).

## 1. Botanical and Geographic Overview

Custard apple (*Annona squamosa* L.), commonly known as sugar apple or sweetsop, is a tropical fruit-bearing tree belonging to the Annonaceae family. It is a small, semi-deciduous tree that typically grows to a height of 3 to 6 meters. The tree is characterized by its pale green, conical, or heart-shaped fruits with a bumpy surface. The fruit is soft, creamy, and sweet, containing numerous seeds embedded in the pulp. The leaves are simple, oblong, and emit a distinct aroma when crushed. It is believed to have originated in the tropical regions of the Americas, particularly the West Indies and northern South America. However, its cultivation has spread across various parts of the world, especially in tropical and subtropical regions (Lakshmi *et al.* 2019). Today, custard apple is widely cultivated in countries such as India, the Philippines, Thailand, Brazil, and parts of Africa and Australia. The plant thrives in warm climates with well-drained soils and is highly drought-tolerant, making it suitable for arid and semi-arid regions. It prefers altitudes ranging from sea level to about 1,500 meters. Its adaptability to different climatic conditions has contributed to its widespread cultivation. The global distribution and adaptability of custard apple make it an important fruit crop with significant agricultural and economic value, particularly in developing regions where it is a staple in local diets (Shukryet *al.* 2019).

## 2. Nutritional Composition and Phytochemical Profile

Custard apple (*Annona squamosa* L.), commonly known as sugar apple or sweetsop, is a tropical fruit highly regarded for its rich nutritional composition and potent phytochemical profile, both of which contribute to its numerous health benefits and medicinal properties. The fruit is a significant source of essential nutrients, including vitamins (particularly vitamin C, B vitamins such as B<sub>1</sub>, B<sub>2</sub>, and B<sub>6</sub>), minerals (potassium, magnesium,

calcium, and phosphorus), and dietary fiber. The high vitamin C content plays a crucial role in bolstering the immune system, enhancing skin health, and providing antioxidant protection against oxidative stress (Pandey *et al.* 2014).

Phytochemically, custard apple is abundant in polyphenols, flavonoids, and acetogenins. Polyphenols, such as catechins and epicatechins, exhibit strong antioxidant and anti-inflammatory properties, which may aid in the prevention of chronic diseases like cardiovascular diseases and cancer. Flavonoids, including quercetin and kaempferol, contribute to the fruit's anti-inflammatory, anti-diabetic, and anti-carcinogenic activities. Acetogenins, unique to the Annonaceae family, have garnered attention for their potential anti-cancer effects, particularly through the inhibition of cancer cell growth and induction of apoptosis (Sampathkumar, 2012).

Furthermore, the presence of essential fatty acids, particularly linoleic and oleic acids, supports heart health by modulating lipid profiles and reducing the risk of atherosclerosis. The fruit's high dietary fiber content aids in digestion, helps regulate blood sugar levels, and contributes to overall gut health. These combined attributes make custard apple a promising candidate for functional foods and nutraceuticals, promoting health and preventing disease (Akram *et al.* 2020).

### **3. Antioxidant Properties and Mechanisms**

Custard apple (*Annona squamosa* L.) is a tropical fruit renowned not only for its unique flavor but also for its potent antioxidant properties, which contribute significantly to its health benefits and medicinal potential. Antioxidants are crucial in neutralizing free radicals, unstable molecules that can cause cellular damage and contribute to the development of chronic diseases, including cancer and cardiovascular conditions. It is rich in polyphenolic compounds, flavonoids, and vitamins C and E, all of which exhibit strong antioxidant activity. These bioactive compounds scavenge free radicals, reducing oxidative stress and thereby protecting cellular components such as DNA, proteins, and lipids from oxidative damage. The fruit's high vitamin C content, in particular, plays a vital role in regenerating other antioxidants within the body, enhancing their overall effectiveness (Varadharaj *et al.* 2014).

The mechanisms underlying the antioxidant action of custard apple involve the inhibition of lipid peroxidation, a process where free radicals attack lipids in cell membranes, leading to cell damage. Additionally, the fruit's compounds upregulate the expression of

antioxidant enzymes, such as superoxide dismutase and catalase, further enhancing the body's defense against oxidative stress. The potent antioxidant properties of custard apple not only support its use as a dietary supplement but also highlight its potential in the prevention and management of oxidative stress-related diseases. These properties, combined with its other medicinal attributes, underscore the value of custard apple in promoting health and preventing disease (Himesh *et al.* 2012).

#### **4. Anti-inflammatory Effects and Their Implications**

Custard apple (*Annona squamosa* L.), commonly known as sugar apple or sweetsop, is a tropical fruit revered not only for its unique flavor but also for its medicinal properties. Among the various health benefits attributed to this fruit, its anti-inflammatory effects have garnered significant attention in recent scientific research. Inflammation is a critical response of the immune system to harmful stimuli, but chronic inflammation is implicated in numerous diseases, including cardiovascular diseases, cancer, and neurodegenerative disorders. The potential of custard apple to mitigate inflammation opens new avenues for its application in therapeutic strategies (Meira *et al.* 2015). The anti-inflammatory effects of custard apple are primarily attributed to its rich phytochemical composition. The fruit contains a variety of bioactive compounds, including flavonoids, alkaloids, and acetogenins, which have been shown to exhibit potent anti-inflammatory activity. Flavonoids, such as quercetin and kaempferol, are known to inhibit the production of pro-inflammatory cytokines and enzymes like cyclooxygenase (COX) and lipoxygenase (LOX). These enzymes play a crucial role in the biosynthesis of inflammatory mediators such as prostaglandins and leukotrienes. By downregulating the activity of these enzymes, flavonoids from custard apple can reduce inflammation at the molecular level (Verma *et al.* 2016).

Acetogenins, another group of compounds found in custard apple, have also demonstrated anti-inflammatory properties by modulating the NF- $\kappa$ B signaling pathway, a key regulator of the inflammatory response. Inhibition of this pathway can lead to a reduction in the expression of inflammatory genes, thereby mitigating chronic inflammation. The implications of these anti-inflammatory effects are profound. Regular consumption of custard apple could potentially aid in the prevention and management of inflammatory diseases. Moreover, its bioactive compounds could be harnessed to develop novel anti-inflammatory drugs or supplements (Balbaa *et al.* 1977). However, while these findings are promising, more clinical studies are needed to fully understand the mechanisms and efficacy of custard apple in human health. The anti-inflammatory properties of custard apple not only enhance its

status as a nutritious fruit but also highlight its potential as a functional food with therapeutic benefits, particularly in combating chronic inflammatory conditions (Pelissier, 1994).

## **5. Role in Cardiovascular Health**

Custard apple, known scientifically as *Annona squamosa* L., has gained recognition for its potential health benefits, particularly in the context of cardiovascular health. This tropical fruit is rich in essential nutrients, including vitamins, minerals, and bioactive compounds, which contribute to its cardioprotective properties. One of the key components of custard apple that plays a significant role in cardiovascular health is its high content of antioxidants, particularly vitamin C, polyphenols, and flavonoids (Thang *et al.* 2013). These compounds help neutralize free radicals, reducing oxidative stress, a major contributor to cardiovascular diseases (CVDs). Oxidative stress can damage the endothelial cells lining blood vessels, leading to atherosclerosis, a condition characterized by the hardening and narrowing of arteries. By mitigating oxidative damage, the antioxidants in custard apple help maintain the integrity of blood vessels, thus lowering the risk of atherosclerosis and related cardiovascular conditions (Kaur *et al.* 2015).

Custard apple is also a good source of dietary fiber, which is known to improve lipid profiles by reducing low-density lipoprotein (LDL) cholesterol levels. Elevated LDL cholesterol is a major risk factor for the development of coronary artery disease. The soluble fiber in custard apple binds to cholesterol in the digestive system, facilitating its excretion and preventing its absorption into the bloodstream. This mechanism not only helps lower LDL cholesterol but also promotes overall heart health (Garg and Gupta, 2005). Furthermore, the presence of potassium in custard apple is beneficial for blood pressure regulation. Potassium acts as a vasodilator, helping to relax blood vessels and reduce the strain on the cardiovascular system. By maintaining healthy blood pressure levels, custard apple contributes to a reduced risk of hypertension, a major risk factor for stroke and heart attack. Its offers a multifaceted approach to cardiovascular health through its rich antioxidant content, cholesterol-lowering properties, and blood pressure regulation. Incorporating custard apple into the diet may therefore be a valuable strategy in the prevention and management of cardiovascular diseases (Rasouli *et al.* 2017).

## **6. Impact on Digestive Health and Gut Microbiome**

Custard apple (*Annona squamosa* L.), a tropical fruit known for its sweet and creamy flesh, has gained attention for its potential benefits on digestive health and the gut

microbiome. The fruit is rich in dietary fiber, vitamins, and bioactive compounds, which contribute to its therapeutic properties. The impact of custard apple on digestive health can be attributed primarily to its high fiber content, which plays a crucial role in maintaining gastrointestinal function (Padhi *et al.* 2011).

Dietary fiber, present in custard apple, facilitates bowel regularity by adding bulk to stools, thus preventing constipation. This natural laxative effect helps in the smooth passage of waste through the digestive tract, reducing the risk of conditions like hemorrhoids and diverticulitis. Additionally, the fiber content aids in the management of irritable bowel syndrome (IBS) by promoting a balanced gut environment. It is also a good source of antioxidants, such as flavonoids, polyphenols, and vitamin C, which help reduce oxidative stress and inflammation in the gastrointestinal tract. Chronic inflammation is a key factor in the development of digestive disorders like inflammatory bowel disease (IBD). The antioxidant properties of custard apple help mitigate this risk, contributing to overall gut health (Reza *et al.* 2009).

Moreover, emerging research suggests that the bioactive compounds in custard apple can positively influence the gut microbiome, the complex community of microorganisms residing in the digestive tract. These compounds act as prebiotics, substances that promote the growth of beneficial gut bacteria. A healthy gut microbiome is essential for optimal digestion, nutrient absorption, and immune function. By modulating the gut microbiota composition, custard apple may help prevent dysbiosis, an imbalance of gut bacteria linked to various digestive and systemic diseases (Ocker and Hopfner, 2012).

Custard apple offers a natural and effective means to support digestive health and maintain a balanced gut microbiome. Its high fiber content, coupled with antioxidant and prebiotic properties, makes it a valuable addition to the diet for those seeking to improve their gastrointestinal well-being. Further research is warranted to fully elucidate the mechanisms through which custard apple influences digestive health and the gut microbiome (Mishra *et al.* 2011).

## **7. Potential in Diabetes Management**

Custard apple (*Annona squamosa* L.), a tropical fruit rich in nutrients and bioactive compounds, has garnered attention for its potential role in diabetes management. This interest stems from its high content of polyphenols, flavonoids, and other phytochemicals, which exhibit antioxidant and anti-inflammatory properties—key factors in the management of

diabetes and its complications. Recent studies have highlighted the hypoglycemic effects of custard apple, attributing them to its ability to enhance insulin secretion and sensitivity. The fruit contains alkaloids such as annonacin, which have been shown to inhibit glucose absorption in the intestine, thereby reducing postprandial blood glucose levels. Moreover, the presence of fiber in custard apple helps in the slow release of glucose into the bloodstream, preventing spikes in blood sugar levels, a common challenge in diabetes management (Alnemari *et al.* 2020).

In addition to its direct effects on blood glucose regulation, custard apple also offers protection against diabetes-induced oxidative stress. The antioxidants present in the fruit, including ascorbic acid and phenolic compounds, neutralize free radicals, thereby reducing oxidative damage to pancreatic  $\beta$ -cells. This preservation of  $\beta$ -cell function is crucial for maintaining insulin production and secretion in diabetic individuals. Furthermore, custard apple's anti-inflammatory properties contribute to its potential in diabetes management. Chronic inflammation is a known contributor to insulin resistance, a hallmark of type 2 diabetes. By modulating inflammatory pathways, the bioactive compounds in custard apple help in reducing insulin resistance and improving glycemic control (Thakkar *et al.* 2011).

Despite these promising findings, more extensive clinical trials are necessary to fully establish the efficacy and safety of custard apple in diabetes management. Future research should focus on isolating specific active compounds, understanding their mechanisms of action, and determining optimal dosages for therapeutic use. In conclusion, custard apple represents a promising natural adjunct in the management of diabetes, offering a multifaceted approach that addresses both glycemic control and the prevention of diabetic complications (Nguyen *et al.* 2020).

## **8. Immune-boosting Properties of Custard Apple**

Custard apple (*Annona squamosa* L.), a tropical fruit rich in nutrients, has been gaining attention for its potential immune-boosting properties. Traditionally valued for its sweet, creamy pulp, the fruit is now recognized as a potent source of bioactive compounds that can enhance the immune system, offering a natural defense against various diseases. The immune-boosting properties of custard apple are largely attributed to its high content of vitamins, particularly vitamin C, which plays a critical role in immune function. Vitamin C is essential for the production and function of white blood cells, which are vital in defending the body against pathogens. It also acts as an antioxidant, protecting immune cells from oxidative stress and enhancing the overall immune response (Kumar *et al.* 2019).

In addition to vitamin C, custard apple is rich in other essential nutrients, such as vitamin B<sub>6</sub>, which supports the production of antibodies and helps maintain the health of the immune system. The presence of dietary fiber in the fruit further contributes to immune health by promoting a healthy gut microbiome. A balanced gut microbiome is crucial for a robust immune system, as it helps regulate immune responses and prevents the overgrowth of harmful pathogens. Moreover, custard apple contains various polyphenols and flavonoids, which exhibit strong antioxidant and anti-inflammatory properties. These compounds help modulate immune responses by reducing inflammation and neutralizing free radicals, thus preventing chronic diseases that can compromise immune function. The anti-inflammatory effects of these bioactive compounds also contribute to the management of conditions such as asthma and allergies, where the immune system plays a key role (Neethu *et al.* 2016).

Research has also shown that the seeds and leaves of custard apple contain acetogenins, which possess immunomodulatory properties. These compounds have been found to enhance the activity of natural killer cells, a type of white blood cell that plays a crucial role in the body's defense against viruses and tumors. It is not only a delicious fruit but also a valuable source of nutrients and bioactive compounds that can support and enhance immune function, making it a promising candidate for functional foods aimed at boosting immunity (Katole *et al.* 2018).

## **9. Anticancer Properties: Current Research and Future Directions**

Custard apple (*Annona squamosa* L.), also known as sugar apple, is a tropical fruit renowned for its nutritional and medicinal benefits. Recent studies have increasingly highlighted its potential anticancer properties, positioning it as a promising candidate for cancer prevention and therapy. Research into the anticancer effects of custard apple has focused on various bioactive compounds found in the fruit, including acetogenins, alkaloids, and flavonoids. Acetogenins, a class of compounds unique to the Annonaceae family, have garnered significant attention due to their cytotoxic effects against cancer cells. These compounds inhibit ATP production in mitochondria, leading to selective toxicity towards cancer cells while sparing normal cells. Recent studies have demonstrated that custard apple acetogenins can induce apoptosis (programmed cell death) in various cancer cell lines, including breast, prostate, and colon cancers (Malik *et al.* 2018).

Additionally, custard apple contains antioxidants such as vitamin C and phenolic compounds that contribute to its anticancer activity. These antioxidants help combat oxidative stress and neutralize free radicals, which are implicated in cancer progression. The fruit's

high fiber content also supports its role in cancer prevention by aiding in digestive health and reducing the risk of colorectal cancer. While current research is promising, there is a need for further investigation to fully elucidate the mechanisms underlying the anticancer effects of custard apple (Luca *et al.* 2020). Future research should focus on conducting clinical trials to validate these findings in human populations and explore the potential synergistic effects of custard apple's bioactive compounds in combination with conventional cancer treatments. Additionally, studies should aim to identify optimal doses and delivery methods to maximize therapeutic benefits. Custard apple exhibits significant potential as a natural anticancer agent. Continued research and clinical trials will be crucial in establishing its efficacy and safety, ultimately paving the way for its integration into cancer prevention and treatment strategies (Panda *et al.* 2015).

## 10. Skin and Hair Health Benefits

Custard apple (*Annona squamosa* L.), commonly known for its sweet, creamy fruit, has garnered attention for its potential skin and hair health benefits. Rich in vitamins, antioxidants, and essential nutrients, this tropical fruit offers a range of therapeutic properties that can enhance dermatological and trichological health (Panda *et al.* 2008).

**Skin Health:** Custard apple is a potent source of vitamin C, a crucial antioxidant that combats oxidative stress and promotes collagen synthesis. Collagen is integral to maintaining skin elasticity and reducing the appearance of wrinkles. The fruit also contains vitamin A, which aids in cellular repair and renewal, contributing to a healthier complexion. Additionally, the presence of antioxidants such as flavonoids and polyphenols help in neutralizing free radicals, thus mitigating premature skin aging and inflammation (Nakano *et al.* 2013).

Moreover, the fruit's high-water content and natural sugars contribute to skin hydration, which is essential for maintaining a supple and smooth texture. Its antimicrobial properties, derived from compounds like annocatalin and annomontacin, can help in treating minor skin infections and acne by reducing bacterial load and inflammation (Davis *et al.* 2012).

**Hair Health:** Custard apple's rich nutritional profile benefits hair health as well. The high vitamin C content supports the production of collagen, which is necessary for strong hair follicles and preventing hair breakage. Vitamin A promotes the health of the scalp by encouraging sebum production, which keeps hair moisturized and reduces dryness and flakiness (Gupta *et al.* 2008).

The fruit's antioxidant properties help in combating oxidative damage to hair cells, which can lead to premature graying and hair loss. Additionally, the essential minerals found in custard apple, such as potassium and magnesium, are vital for maintaining healthy hair growth and preventing scalp issues. Incorporating custard apple into one's diet can offer significant benefits for skin and hair health. Its rich array of vitamins, antioxidants, and minerals provides comprehensive support for maintaining youthful skin and strong, vibrant hair, making it a valuable addition to a health-conscious lifestyle (Ranjana *et al.* 2014).

## **11. Traditional Medicinal Uses Across Cultures**

Custard Apple (*Annona squamosa* L.), commonly known for its sweet and creamy flesh, has been utilized in traditional medicine across diverse cultures for centuries. Its medicinal properties are deeply rooted in the practices of many traditional healing systems. In Ayurvedic medicine, the custard apple is valued for its cooling properties and is used to treat a variety of ailments. The fruit is believed to balance the body's doshas, particularly Pitta and Kapha. Its seeds are used in poultices to relieve joint pain and as a remedy for parasitic infections. The leaf extracts are employed for their anti-inflammatory and antidiabetic effects, aiding in the management of conditions such as diabetes and hypertension (Quilez *et al.* 2018).

In traditional Chinese medicine (TCM), custard apple is recognized for its nourishing qualities. The fruit is consumed to enhance vitality and support digestive health. Its seeds and leaves are used in TCM practices to treat coughs and respiratory issues. The plant's adaptogenic properties are believed to help the body adapt to stress and improve overall resilience. In South American and Caribbean traditional medicine, custard apple is celebrated for its potential in treating digestive disorders. The fruit and its components are used to alleviate gastrointestinal discomforts and to enhance digestive function. Additionally, custard apple is used in folk remedies to address skin conditions and to promote wound healing due to its antimicrobial properties (Wang *et al.* 2014).

African traditional medicine also utilizes various parts of the custard apple tree. The bark and leaves are used in decoctions for their purported antimalarial and anti-inflammatory effects. The fruit's nutritional value, combined with its medicinal properties, makes it a versatile component in traditional African healing practices. Overall, Custard Apple (*Annona squamosa* L.) has played a significant role in traditional medicine systems worldwide, reflecting its broad therapeutic potential and cultural significance. The integration of custard apple in these diverse medicinal practices highlights its importance as both a food and a

remedy, warranting further scientific investigation to validate and expand upon these traditional uses (Eadhollyet *al.* 2019).

## **12. Pharmacological Activities of Custard Apple Extracts**

Custard apple (*Annona squamosa* L.), also known as sugar apple, is a tropical fruit with notable pharmacological activities attributed to its bioactive compounds. Research into the pharmacological effects of custard apple extracts has highlighted its potential therapeutic benefits, particularly in the realms of anti-inflammatory, antioxidant, and antimicrobial activities. Pharmacological investigations have demonstrated that custard apple extracts possess significant anti-inflammatory properties (Al-Malki *et al.* 2015). Studies reveal that the extracts can inhibit pro-inflammatory cytokines and enzymes, such as cyclooxygenase-2 (COX-2), thereby mitigating inflammation-related conditions. This anti-inflammatory effect is largely attributed to the presence of various polyphenols and flavonoids in the fruit, which modulate inflammatory pathways. Additionally, custard apple extracts exhibit potent antioxidant activity. The fruit's rich polyphenolic content, including flavonoids and tannins, contributes to its ability to neutralize free radicals and reduce oxidative stress. This antioxidant capacity is crucial in preventing cellular damage and may play a role in lowering the risk of chronic diseases, such as cardiovascular disorders and certain cancers (Ruddarajuet *al.* 2019).

Antimicrobial properties of custard apple extracts have also been extensively studied. The fruit's extracts demonstrate effectiveness against various pathogenic microorganisms, including bacteria and fungi. This antimicrobial activity is attributed to the presence of essential oils and alkaloids, which disrupt microbial cell membranes and inhibit growth. Moreover, custard apple extracts have shown potential in glucose regulation and anti-diabetic effects (Seyfried and Huysentruyt, 2013). Some studies suggest that extracts can enhance insulin sensitivity and reduce blood glucose levels, which may benefit individuals with diabetes or metabolic syndrome. Custard apple (*Annona squamosa* L.) extracts exhibit a range of pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, and potential anti-diabetic effects. These properties underscore the fruit's potential as a natural therapeutic agent and highlight the importance of further research to fully elucidate its medicinal benefits and applications (Kulkarni *et al.* 2011).

## **13. Future Prospects in Nutraceutical and Pharmaceutical Applications**

Custard apple (*Annona squamosa* L.), also known as sweetsop, has long been recognized for its nutritional value and medicinal properties. Recent research highlights its potential in nutraceutical and pharmaceutical applications, offering promising avenues for future development. The fruit is rich in essential nutrients, including vitamins A and C, potassium, and dietary fiber, which contribute to its antioxidant, anti-inflammatory, and immunomodulatory properties. These attributes position custard apple as a valuable component in dietary supplements aimed at enhancing overall health and preventing chronic diseases (Shenoy *et al.* 2009).

In the realm of nutraceuticals, custard apple's bioactive compounds, such as annonaceous acetogenins, have demonstrated significant potential. These compounds exhibit potent antioxidant and anticancer activities, suggesting possible roles in preventing or managing cancer. Their ability to target cancer cells while sparing normal cells makes them attractive candidates for development into novel anticancer agents. Additionally, custard apple's high fiber content and low glycemic index present opportunities for its use in managing metabolic disorders such as diabetes and obesity. Functional foods and supplements incorporating custard apple could support blood sugar regulation and weight management, contributing to the prevention and management of type 2 diabetes and related conditions (Gowdhami *et al.* 2014).

Pharmaceutical applications are also promising. Extracts from custard apple have shown potential in antimicrobial and antiviral activities, which could lead to the development of new treatments for infectious diseases. Furthermore, ongoing research into its neuroprotective effects suggests that custard apple could play a role in combating neurodegenerative diseases, such as Alzheimer's disease, by reducing oxidative stress and inflammation in the brain (Asharani *et al.* 2009).

Future research should focus on clinical trials to validate these benefits and optimize extraction methods to enhance the bioavailability and efficacy of custard apple's active compounds. Additionally, exploring sustainable cultivation practices will be crucial to ensure a steady supply of high-quality raw materials. Custard apple holds substantial promise in the fields of nutraceuticals and pharmaceuticals. Its diverse health benefits and medicinal properties warrant further investigation to unlock its full potential and improve human health outcomes (Gupta *et al.* 2005).

## **CONCLUSION**

Custard Apple (*Annona squamosa* L.) demonstrates a significant potential for promoting health and treating various ailments due to its rich nutritional and medicinal profile. Its high content of vitamins, particularly vitamin C, and essential minerals such as potassium and magnesium, contributes to its antioxidant properties, supporting overall immune health and reducing oxidative stress. Additionally, the presence of bioactive compounds like acetogenins in Custard Apple exhibits promising anticancer and antimicrobial activities, suggesting its utility in complementary cancer therapy and infection management. The fruit's dietary fiber aids in digestive health by promoting regular bowel movements and preventing constipation. Traditional uses and emerging research highlight its potential in managing chronic conditions, including hypertension and diabetes, due to its ability to regulate blood sugar levels and improve cardiovascular health. However, while the benefits are substantial, further clinical trials and rigorous research are necessary to substantiate these findings and establish optimal therapeutic protocols. Integrating Custard Apple into dietary and medicinal practices could offer a valuable natural adjunct to modern health strategies, emphasizing the need for continued exploration of its full therapeutic potential.

## REFERENCE

1. Kalidindi, N.; Thimmaiah, N.V.; Jagadeesh, N.V.; Nandeep, R.; Swetha, S.; Kalidindi, B. Antifungal and antioxidant activities of organic and aqueous extracts of *Annona squamosa* Linn. leaves. *J. Food Drug Anal.* **2015**, *23*, 795–802.
2. Anaya-Esparza, L.M.; de Lourdes García-Magaña, M.; Abraham Domínguez-Ávila, J.; Yahia, E.M.; Salazar-López, N.J.; González-Aguilar, G.A.; Montalvo-González, E. Annonas: Underutilized species as a potential source of bioactive compounds. *Food Res. Int.* **2020**, 138.
3. El-Chaghaby, G.A.; Ahmad, A.F.; Ramis, E.S. Evaluation of the antioxidant and antibacterial properties of various solvents extracts of *Annona squamosa* L. leaves. *Arab. J. Chem.* **2014**, *7*, 227–233.
4. Sundaramahalingam, M.A.; Karthikumar, S.; Shyam Kumar, R.; Samuel, K.J.; Shajahan, S.; Sivasubramanian, V.; Sivashanmugam, P.; Varalakshmi, P.; Syed, A.; Marraiki, N.; et al. An intensified approach for transesterification of biodiesel from *Annona squamosa* seed oil using ultrasound-assisted homogeneous catalysis reaction and its process optimization. *Fuel* **2021**, *291*, 120195.
5. Zahid, M.; Mujahid, M.; Singh, P.K.; Farooqui, S.; Singh, K.; Parveen, S.; Arif, M. *Annona squamosa* linn. (Custard apple): An aromatic medicinal plant fruit with

- immense nutraceutical and therapeutic potentials (Review). *Int. J. Pharm. Sci. Res.* **2018**, 9, 1745–1759.
6. Kumar, M.; Dahuja, A.; Sachdev, A.; Kaur, C.; Varghese, E.; Saha, S.; Sairam, K.V.S.S. Valorisation of black carrot pomace: Microwave assisted extraction of bioactive phytochemicals and antioxidant activity using Box–Behnken design. *J. Food Sci. Technol.* **2019**, 56, 995–1007.
  7. Kumar, M.; Dahuja, A.; Sachdev, A.; Kaur, C.; Varghese, E.; Saha, S.; Sairam, K.V.S.S. Evaluation of enzyme and microwave-assisted conditions on extraction of anthocyanins and total phenolics from black soybean (*Glycine max* L.) seed coat. *Int. J. Biol. Macromol.* **2019**, 135, 1070–1081.
  8. Punia, S.; Sandhu, K.S.; Grasso, S.; Purewal, S.S.; Kaur, M.; Siroha, A.K.; Kumar, K.; Kumar, V.; Kumar, M. *Aspergillus oryzae* fermented rice bran: A byproduct with enhanced bioactive compounds and antioxidant potential. *Foods* **2021**, 10, 70.
  9. Kumar, M.; Tomar, M.; Amarowicz, R.; Saurabh, V.; Nair, M.S.; Maheshwari, C.; Sasi, M.; Prajapati, U.; Hasan, M.; Singh, S.; Guava (*Psidium guajava* L.) Leaves: Nutritional Composition, Phytochemical Profile, and Health-Promoting Bioactivities. *Foods* **2021**, 10, 752. [CrossRef]
  10. Kumar, M.; Dahuja, A.; Sachdev, A.; Kaur, C.; Varghese, E.; Saha, S.; Sairam, K.V.S.S. Black Carrot (*Daucus carota* ssp.) and Black Soybean (*Glycine max* (L.) Merr.) Anthocyanin Extract: A Remedy to Enhance Stability and Functionality of Fruit Juices by Copigmentation. *Waste Biomass Valorization* **2020**, 11, 99–108.
  11. Kumar, M.; Tomar, M.; Punia, S.; Amarowicz, R.; Kaur, C. Evaluation of cellulolytic enzyme-assisted microwave extraction of *Punica granatum* peel phenolics and antioxidant Activity. *Plant Foods Hum. Nutr.* **2020**, 75, 614–620.
  12. Nishad, J.; Dutta, A.; Saha, S.; Rudra, S.G.; Varghese, E.; Sharma, R.R.; Tomar, M.; Kumar, M.; Kaur, C. Ultrasound-assisted development of stable grapefruit peel polyphenolic nano-emulsion: Optimization and application in improving oxidative stability of mustard oil. *Food Chem.* **2021**, 334.
  13. Kumar, M.; Potkule, J.; Patil, S.; Saxena, S.; Patil, P.G.; Mageshwaran, V.; Punia, S.; Varghese, E.; Mahapatra, A.; Ashtaputre, N.; et al. Extraction of ultra-low gossypol protein from cottonseed: Characterization based on antioxidant activity, structural morphology and functional group analysis. *LWT* **2021**, 140, 110692.

14. Kumar, M.; Tomar, M.; Punia, S.; Grasso, S.; Arrutia, F.; Choudhary, J.; Singh, S.; Verma, P.; Mahapatra, A.; Patil, S.; Cottonseed: A sustainable contributor to global protein requirements. *Trends Food Sci. Technol.* **2021**, *111*, 100–113.
15. Kumar, M.; Potkule, J.; Tomar, M.; Punia, S.; Singh, S.; Patil, S.; Singh, S.; Ilakiya, T.; Kaur, C.; Kennedy, J.F. Jackfruit seed slimy sheath, a novel source of pectin: Studies on antioxidant activity, functional group, and structural morphology. *Carbohydr. Polym. Technol. Appl.* **2021**, *2*, 100054.
16. Kumar, M.; Dahuja, A.; Tiwari, S.; Punia, S.; Tak, Y.; Amarowicz, R.; Bhoite, A.G.; Singh, S.; Joshi, S.; Panesar, P.S.; et al. Recent trends in extraction of plant bioactives using green technologies: A review. *Food Chem.* **2021**, *353*, 129431.
17. Punia, S.; Kumar, M. Litchi (*Litchi chinensis*) seed: Nutritional profile, bioactivities, and its industrial applications. *Trends Food Sci. Technol.* **2021**, *108*, 58–70.
18. Al-Nemari, R.; Al-Senaigy, A.; Semlali, A.; Ismael, M.; Badjah-Hadj-Ahmed, A.Y.; Ben Bacha, A. GC-MS profiling and assessment of antioxidant, antibacterial, and anticancer properties of extracts of *Annona squamosa* L. leaves. *BMC Complement. Med. Ther.* **2020**, *20*, 1–14.
19. Mannino, G.; Gentile, C.; Porcu, A.; Agliassa, C.; Caradonna, F.; Berteà, C.M. Chemical profile and biological activity of cherimoya (*Annona cherimola* Mill.) and atemoya (*Annona atemoya*) leaves. *Molecules* **2020**, *25*, 2612.
20. Hosseinabadi, T. The Medicinal Importance of *Annona squamosa* fruits. *J. Explor. Res. Pharmacol.* **2021**.
21. Lakshmi Kalyani, R.; Chandra, V.S.; Vijaykumar, P.P.N.; Pammi, S.V.N.; Rajkumar, M.; Swamy, P.V.; Murthy, K.V.R. Biosynthesis of silver nanoparticles using *Annona squamosa* leaf extract with synergistic antibacterial activity. *Indian J. Pharm. Sci.* **2019**, *81*, 1036–1044.
22. Shukry, W.M.; Galilah, D.A.; Elrazek, A.A. Mineral Composition, Nutritional Properties, Vitamins, and Bioactive Compounds in *Annona squamosa* L. grown at different sites of Egypt. *Ser. Bot. Environ. Sci.* **2019**, *1*, 7–22.
23. Pandey, V.K.; Giri, I.C.; Singh, P.; Srivastava, A. Pharmacognostical and physiochemical study on the leaves of *Annona squamosa* Linn. *Int. J. Res. Pharm. Sci.* **2014**, *4*, 8–12.
24. Sampathkumar, P. Phytochemical screening and antimicrobial activity of plant extracts for disease management. *Int. J. Curr. Sci.* **2012**, *2012*, 209–218.

25. Akram, M.; Munir, N.; Daniyal, M.; Egbuna, C.; Gaman, M.A.; Onyekere, P.F.; Olatunde, A. Vitamins and Minerals: Types, sources and their functions. In *Functional Foods and Nutraceuticals*; Springer International Publishing: Berlin/Heidelberg, Germany, 2020; 149–172.
26. Varadharaj, V.; Janarthanan, U.D.; Krishnamurthy, V.; Synnah, J. Assessment of Phytonutrients in the Ethanolic Leaf Extract of *Annona Squamosa* (L.). *World J. Pharm. Pharm. Sci.* **2014**, *3*, 725–732.
27. Himesh, S.; Singhai, A.K.; Sarvesh, S. Quantification of ascorbic acid in leaves of *Annona squamosa*. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 144–147.
28. Meira, C.S.; Guimarães, E.T.; Macedo, T.S.; da Silva, T.B.; Menezes, L.R.A.; Costa, E.V.; Soares, M.B.P. Chemical composition of essential oils from *Annona vepretorum* Mart. and *Annona squamosa* L. (Annonaceae) leaves and their antimalarial and trypanocidal activities. *J. Essent. Oil Res.* **2015**, *27*, 160–168.
29. Verma, R.S.; Joshi, N.; Padalia, R.C.; Singh, V.R.; Goswami, P.; Chauhan, A. Characterization of the Leaf Essential Oil Composition of *Annona squamosa* L. from Foothills of North India. *Med. Aromat. Plants* **2016**, *5*.
30. Balbaa, S.I.; Haggag, M.Y.; Taha, K.F. Study of volatile oil content of the leaves of *Annona squamosa* L. growing in Egypt. *Egypt. J. Pharm. Sci.* **1977**.
31. Péliissier, Y.; Marion, C.; Kone, D.; Lamaty, G.; Menut, C.; Bessière, J.M. Volatile components of *Annona muricata* L. *J. Essent. Oil Res.* **1994**, *6*, 411–414.
32. Thang, T.D.; Dai, D.N.; Hoi, T.M.; Ogunwande, I.A. Study on the volatile oil contents of *Annona glabra* L., *Annona squamosa* L., *Annona muricata* L. and *Annona reticulata* L., from Vietnam. *Nat. Prod. Res.* **2013**, *27*, 1232–1236.
33. Kaur, R.; Kaur, K.; Kaur, P.; Singh, I. Sitaphal: Unexplored therapeutic potential. *Asian J. Res. Chem. Pharm. Sci.* **2015**, *3*, 129–141.
34. Garg, S.N.; Gupta, D. Composition of the leaf oil of *Annona squamosa* L. From the north indian plains. *J. Essent. Oil Res.* **2005**, *17*, 257–258.
35. Rasouli, H.; Farzaei, M.H.; Khodarahmi, R. Polyphenols and their benefits: A review. *Int. J. Food Prop.* **2017**, *20*, 1700–1741.
36. Padhi, L.P.; Panda, S.K.; Satapathy, S.N.; Dutta, S.K. In vitro evaluation of antibacterial potential of *Annona squamosa* L. and *Annona reticulata* L. from Similipal Biosphere Reserve. *J. Agric. Technol.* **2011**, *7*, 133–142.
37. Reza, A.; Mazahery, F.; Dator, R.P.; Concepcion, G.P.; Jacinto, S.D. Murihexocin C from the Leaves of *Annona squamosa* Linn. Murihexocin C from the Leaves of

- Annona squamosa* Linn. Induces Apoptosis in Human Colon Carcinoma Col 2 Cell Line. *Philipp. Agric. Sci.* **2009**, 92.
38. Ocker, M.; Höpfner, M. Apoptosis-modulating drugs for improved cancer therapy. *Eur. Surg. Res.* **2012**.
39. Mishra, B.B.; Tiwari, V.K. Natural products: An evolving role in future drug discovery. *Eur. J. Med. Chem.* **2011**.
40. Al-nemari, R.; Bacha, A.B.; Al-senaidey, A.; Arafah, M.; Al-saran, H. Selective cytotoxic effects of *Annona Squamosa* Leaves against breast cancer cells via apoptotic signaling proteins. *Preprints* **2020**, 1–14.
41. Thakkar, J.H.; Solanki, H.K.; Tripathi, P.; Patel, N.J.; Jani, G.K. Evaluation of antimutagenic potential of *Annona squamosa* leaf extract. *Elixir Hum. Physiol.* **2011**, 31, 1960–1965.
42. Nguyen, M.T.; Nguyen, T.; Le, V.M.; Trieu, L.H.; Lam, T.D.; Bui, L.M.; Nhan, L.T.H.; Danh, V.T. Assessment of preliminary phytochemical screening, polyphenol content, flavonoid content, and antioxidant activity of custard apple leaves (*Annona squamosa* Linn.). *IOP Conf. Ser. Mater. Sci. Eng.* **2020**, 736.
43. Kumar, Y.; Kumar Chandra, B.A.G.; Gajera, H.H.; Kumar Chandra, A.; Yashwant Kumar, C.; Gajera, H.H. Evaluation of antidiabetic and antioxidant potential of custard apple (*Annona squamosa*) Leaf extracts: A compositional study. *Int. J. Chem. Stud.* **2019**, 7.
44. Neethu, S.K.; Santhoshkumar, R.; Kumar, N.S. Phytochemical analysis and antimicrobial activities of *Annona squamosa* (L) leaf extracts. *J. Pharmacogn. Phytochem.* **2016**, 5, 128–131.
45. Katole, R.; Gautam, J.; Mokate, D. Phytochemical study of *Annona squamosa* L. and *Annona reticulata* L. *Int. J. Res.* **2018**, 5.
46. Malik, J.; Gandhi, R.; Vishwavidyalaya, P.; Soni, H.; Yadav, A.P.; Yadav, B. Characterization of rutin isolated by leaves *Annona squamosa* by modern analytical techniques. *Eur. J. Biomed. Pharm. Sci.* **2018**, 5, 484–489.
47. Luca, S.V.; Macovei, I.; Bujor, A.; Miron, A.; Skalicka-Woźniak, K.; Aprotosoiaie, A.C.; Trifan, A. Bioactivity of dietary polyphenols: The role of metabolites. *Crit. Rev. Food Sci. Nutr.* **2020**, 60, 626–659.
48. Panda, S.; Kar, A. Protective effects of 5,7,40-trihydroxy-6,30dimethoxy-flavone 5-O- $\beta$ -l-rhamnopyranoside, isolated from *Annona squamosa* leaves in thyrotoxicosis and

- in hepatic lipid peroxidation in rats. *Bioorganic Med. Chem. Lett.* **2015**, *25*, 5726–5728.
49. Panda, S.; Kar, A. Antidiabetic and antioxidative effects of *Annona squamosa* leaves are possibly mediated through quercetin-3-Oglucoside. *BioFactors* **2008**, *31*, 201–210.
50. Nakano, D.; Ishitsuka, K.; Kamikawa, M.; Matsuda, M.; Tsuchihashi, R.; Okawa, M.; Okabe, H.; Tamura, K.; Kinjo, J. Screening of promising chemotherapeutic candidates from plants against human adult T-cell leukemia/lymphoma (III). *J. Nat. Med.* **2013**, *67*, 894–903. [CrossRef]
51. Davis, J.A.; Sharma, S.; Mitra, S.; Sujatha, S.; Kanaujia, A.; Shukla, G.; Katiyar, C.; Lakshmi, B.S.; Bansal, V.S.; Bhatnagar, P.K. Antihyperglycemic effect of *Annona squamosa* hexane extract in type 2 diabetes animal model: PTP1B inhibition, a possible mechanism of action. *Indian J. Pharmacol.* **2012**, *44*, 326–332.
52. Gupta, R.K.; Kesari, A.N.; Diwakar, S.; Tyagi, A.; Tandon, V.; Chandra, R.; Watal, G. In vivo evaluation of anti-oxidant and anti-lipidemic potential of *Annona squamosa* aqueous extract in Type 2 diabetic models. *J. Ethnopharmacol.* **2008**, *118*, 21–25.
53. Ranjana; Tripathi, Y.B. Insulin secreting and  $\alpha$ -glucosidase inhibitory activity of hexane extract of *Annona squamosa* Linn. in streptozotocin (STZ) induced diabetic rats. *Indian J. Exp. Biol.* **2014**, *52*, 623–629.
54. Quílez, A.M.; Fernández-Arche, M.A.; García-Giménez, M.D.; De la Puerta, R. Potential therapeutic applications of the genus *Annona*: Local and traditional uses and pharmacology. *J. Ethnopharmacol.* **2018**, *225*, 244–270.
55. Wang, D.S.; Rizwani, G.H.; Guo, H.; Ahmed, M.; Ahmed, M.; Hassan, S.Z.; Hassan, A.; Chen, Z.S.; Xu, R.H. *Annona squamosa* Linn: Cytotoxic activity found in leaf extract against human tumor cell lines. *Pak. J. Pharm. Sci.* **2014**, *27*, 1559–1563.
56. Fadholly, A.; Proboningrat, A.; Dewi Iskandar, R.; Rantam, F.; Sudjarwo, S. In vitro anticancer activity *Annona squamosa* extract nanoparticle on WiDr cells. *J. Adv. Pharm. Technol. Res.* **2019**, *10*, 149–154.
57. Al-Malki, A.L.; El Rabey, H.A. The Antidiabetic Effect of Low Doses of *Moringa oleifera* Lam. Seeds on Streptozotocin Induced Diabetes and Diabetic Nephropathy in Male Rats. *Biomed Res. Int.* **2015**, *2015*, 1–13.
58. Ruddaraju, L.K.; Pallela, P.N.V.K.; Pammi, S.V.N.; Padavala, V.S.; Kolapalli, V.R.M. Synergetic antibacterial and anticarcinogenic effects of *Annona squamosa* leaf extract mediated silver nano particles. *Mater. Sci. Semicond. Process.* **2019**, *100*, 301–309.

59. Seyfried, T.N.; Huysentruyt, L.C. On the origin of cancer metastasis. *Crit. Rev. Oncog.* **2013**.
60. Kulkarni, V.R.; Chandrashekar, C. Isolation, Characterizations and Free radical scavenging activity of *Annona squamosa* leaf. *J. Pharm. Res.* **2011**, *4*, 610–611.
61. Shenoy, C.; Patil, M.B.; Kumar, R. Antibacterial and wound healing activity of the leaves of *Annona squamosa* Linn. (*Annonaceae*). *Res. J. Pharmacogn. Phytochem.* **2009**, *1*, 44–50.
62. Gowdhami, M.; Sarkar, B.L.; Ayyasamy, P.M. Screening of Phytochemicals and Antibacterial Activity of *Annona Squamosa* Extracts. *Int. J. Pharm. Sci. Invent.* **2014**, *3*, 30–39.
63. AshaRani, P.V.; Mun, G.L.K.; Hande, M.P.; Valiyaveetil, S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. *ACS Nano* **2009**.
64. Gupta, R.K.; Kesari, A.N.; Murthy, P.S.; Chandra, R.; Tandon, V.; Watal, G.; Gupta, R.K.; Kesari, A.N.; Murthy, P.S.; Chandra, R.; et al. Hypoglycemic and antidiabetic effect of ethanolic extract of leaves of *Annona squamosa* L. in experimental animals. *J. Ethnopharmacol.* **2005**, *99*, 75–81.
65. Kaleem, M.; Asif, M.; Ahmed, Q.U.; Bano, B. Antidiabetic and antioxidant activity of *Annona squamosa* extract in streptozotocin-induced diabetic rats. *Singapore Med. J.* **2006**, *47*, 670–675.
66. Shirwaikar, A.; Rajendran, K.; Kumar, C.D.; Bodla, R. Antidiabetic activity of aqueous leaf extract of *Annona squamosa* in streptozotocin-nicotinamide type 2 diabetic rats. *J. Ethnopharmacol.* **2004**, *91*, 171–175.
67. Sonkar, N.; Yadav, A.K.; Mishra, P.K.; Jain, P.K.; Rao, C.V. Evaluation of hepatoprotective activity of *Annona squamosa* leaves and bark extract against carbon tetrachloride liver damage in wistar rats. *World J. Pharm. Pharm. Sci.* **2016**, *5*, 1353–1360.
68. Shirwaikar, A.; Rajendran, K.; Kumar, C.D. Oral antidiabetic activity of *Annona squamosa* leaf alcohol extract in NIDDM rats. *Pharm. Biol.* **2004**, *42*, 30–35.
69. Sobiya Raj, D.; Vennila, J.J.; Aiyavu, C.; Panneerselvam, K. The hepatoprotective effect of alcoholic extract of *Annona squamosa* leaves on experimentally induced liver injury in swiss albino mice. *Int. J. Integr. Biol.* **2009**, *5*, 182–186.
70. El-baz, D.M.; Hssan, A.K. Effects of Egyptian *Annona squamosa* leaves extracts against alloxan induced hyperglycemia in rats. *World J. Pharm. Pharm. Sci.* **2019**, *8*, 145–163.

71. Rajeshkumar, A.; Tamilarasan, B.; Sivakumar, V. Phytochemical screening and hepatoprotective efficacy of leaves extracts of annona squamosa against paracetamol induced liver Toxicity in rats. *Int. J. Pharmacogn.* **2015**, *22*, 178–185.
72. Ibrahim, F.; Jaber, A.; Ibrahim, G.; Cheble, E. Antioxidant activity and total phenol content of different plant parts of Lebanese Annona Squamosa Linn. *Int. J. Pharm. Pharm. Sci.* **2020**, 100–105.
73. Halliwell, B.; Gutteridge, J.M.C. Role of free radicals and catalytic metal ions in human disease: An overview. *Methods Enzymol.* **1990**, *186*, 1–85.
74. Gajalakshmi, S.; Vijayalakshmi, S.; Devi Rajeswari, V. Phytochemical and pharmacological properties of Annona muricata: A review. *Int. J. Pharm. Pharm. Sci.* **2012**, *4*, 3–6.
75. Sharma, S.K.; Gupta, M.L.; Kumar, B. Hypocholesterolemic Efficacy of Annona Squamosa (L.) Extract In Mice Diabetic Models. *J. Biotechnol. Biochem.* **2019**, *5*, 41–45.
76. Tomar, R.S.; Sisodia, S.S. Antidiabetic activity of Annona squamosa Linn. in alloxan-induced diabetic rats. *Int. J. Green Pharm.* **2014**, *8*, 237–241.
77. Pandey, N.; Barve, D. Phytochemical and pharmacological review on Annona squamosa Linn. *Int. J. Res. Pharm. Biomed. Sci.* **2011**, *2*, 1404–1412.
78. Wu, Y.C.; Hung, Y.C.; Chang, F.R.; Cosentino, M.; Wang, H.K.; Lee, K.H. Identification of ent-16,17-dihydroxykauran-19-oic acid as an anti- HIV principle and isolation of the new diterpenoids annosquamosins A and B from Annona squamosa. *J. Nat. Prod.* **1996**, *59*, 635–637.
79. Chandra, H.; Bishnoi, P.; Yadav, A.; Patni, B.; Prakash Mishra, A.; Nautiyal, A.R.; Mishra, A.P.; Nautiyal, A.R.; Prakash Mishra, A.; Nautiyal, A.R. Antimicrobial resistance and the alternative resources with special emphasis on plant-based antimicrobials—A review. *Plants* **2017**, *6*, 16.
80. Nandita, H.; Manohar, M.; Gowda, D.V. Recent review on oxidative stress, cellular senescence and age-associated diseases. *Int. J. Res. Pharm. Sci.* **2020**, *11*, 1331–1342.
81. Ola, A.R.B.; Sugi, Y.; Lay, C.S. Isolation, identification and antimicrobial activity of secondary metabolites of endophytic fungi from annona leaves (Annona squamosa L.) growing in dry land. *IOP Conf. Ser. Mater. Sci. Eng.* **2020**, *823*, 012039.
82. Kurutas, E.B. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: Current state. *Nutr. J.* **2016**, *15*, 1–22.

83. Fang-nan, K.O.; Wen-yan, L.I.; You, W.E.; Jing, Z.H.; Jing, Z.H.; Zhi-qiang, Y.A.; Xiu-fen, Z. Optimization of Extraction Process of Polyphenols from *Annona squamosa* Leaves and Its Antioxidant Activity in Vitro. *Sci. Technol. Food Ind.* **2020**, *41*, 162–168.
84. Babu Marahatta, A.; Aryal, A.; Chandra Basnyat, R.; Anant Babu Marahatta, C. The phytochemical and nutritional analysis and biological activity of *Annona squamosa* Linn. *Int. J. Herb. Med.* **2019**, *7*, 19–28.
85. Cosentino, S.; Tuberoso, C.I.G.G.; Pisano, B.; Satta, M.; Mascia, V.; Arzedi, E.; Palmas, F. In-vitro antimicrobial activity and chemical composition of Sardinian *Thymus* essential oils. *Lett. Appl. Microbiol.* **1999**, *29*, 130–135.
86. Shanker, K.S.; Kanjilal, S.; Rao, B.V.S.K.; Kishore, K.H.; Misra, S.; Prasad, R.B.N. Isolation and antimicrobial evaluation of isomeric hydroxy ketones in leaf cuticular waxes of *Annona squamosa*. *Phytochem. Anal.* **2007**, *18*, 7–12.
87. Dholvitayakhun, A.; Trachoo, N.; Sakee, U.; Cushnie, T.P.T.T. Potential applications for *Annona squamosa* leaf extract in the treatment and prevention of foodborne bacterial disease. *Nat. Prod. Commun.* **2013**, *8*, 1934–1948.
88. Uduman, M.S.T.S.; Sundarapandian, R.; Muthumanikkam, A.; Kalimuthu, G.; Parameswari, S.A.; Srinivas, T.R.V.; Karunakaran, G. Protective effect of methanolic extract of *Annona squamosa* linn in isoniazid-rifampicin induced hepatotoxicity in rats. *Pak. J. Pharm. Sci.* **2011**, *24*, 129–134.