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Exploring the Phytochemistry and Pharmacological Potentials of *Annona squamosa* L. : A Systematic Review of Traditional Uses and Modern Applications

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Abstract *— Annona squamosa* L. (Annonaceae) is a tropical evergreen fruit tree with a long history of traditional use across various cultures. Its fruit, known as srikayas, is commonly consumed fresh and used in candies, ice creams, and beverages. Different parts of *A. squamosa* have been widely applied in ethnomedicine as tonics, apophlegmatisants, coolants, abortifacients, and heart sedatives. Phytochemical studies have identified key bioactive compounds including annonaceous acetogenins (ACGs), diterpenes (DITs), alkaloids (ALKs), and cyclopeptides (CPs), with 33 diterpenes, 19 alkaloids, 88 acetogenins, and 13 cyclopeptides reported up to 2016. Extensive research reveals *A. squamosa* exhibits diverse pharmacological activities such as anticancer, antioxidant, antidiabetic, antihypertensive, hepatoprotective, antiparasitic, antimalarial, insecticidal, microbicidal, and molluscicidal effects. Notably, diterpenes and acetogenins contribute to its potent anticancer properties through apoptosis induction and cell cycle arrest. Leaf and seed extracts demonstrate significant antidiabetic, anti-inflammatory, and hepatoprotective actions, while seed peptides exhibit vasorelaxant and hypotensive effects via calcium channel inhibition. This review integrates phytochemical, ethnopharmacological, and bioactivity data, highlighting the therapeutic potential of *A. squamosa* and encouraging further clinical studies to validate its medicinal applications.

Keywords *— Annona squamosa;* Phytochemicals; Bioactivity

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INTRODUCTION

Annona squamosa L., commonly known as custard apple or sugar apple, is a tropical fruit-bearing plant of the Annonaceae family, widely cultivated in Southeast Asia, India, South America, and Africa [1-2]. Traditionally, various parts of the plant—including leaves, seeds, bark, and fruits—have been used in folk medicine to treat ailments such as diarrhea, dysentery, skin infections, diabetes, hypertension, and wounds, reflecting its cultural and therapeutic importance across regions like India, Thailand, and Indonesia [1,3].

Phytochemical investigations reveal a diverse array of bioactive compounds, including alkaloids, flavonoids, terpenoids, phenolics, tannins, and notably annonaceous acetogenins, which possess cytotoxic, antitumor, and mitochondrial inhibitory activities, making them promising candidates for anticancer drug development [4]. Ethanol extracts of leaves and seeds demonstrate strong antioxidant activities by scavenging free radicals and enhancing endogenous enzymatic defense systems [5]. Moreover, *A. squamosa* exhibits significant antidiabetic potential, with leaf and fruit extracts improving insulin sensitivity and lowering blood glucose through α-glucosidase inhibition and GLUT-4 upregulation [6].

Bark and seed extracts also show antimicrobial activity against pathogens like *Staphylococcus aureus* and *Escherichia coli,* along with anti-inflammatory and immunomodulatory effects [7]. Despite growing research on its bioactivities and phytochemistry, comprehensive reviews integrating traditional knowledge and pharmacological evidence remain limited. This systematic review consolidates recent findings on the phytochemical composition and biological activities of *A. squamosa ,* providing a scientific basis for its development as a phytopharmaceutical and functional food ingredient [1,4-5]. The genus Annona includes around 125 species, many cultivated for edible fruits, with *A. squamosa* being a prominent species known by various common names including sugar apple, sweetsop, and custard apple [8-9].

Kingdom	Plantae
Subkingdom	Tracheobionta (vascular plants)
Superdivision	Spermatophyta (seed plants)
Division	Magnoliophyta (flowering plants)
Class	Magnoliopsida (dicotyledons)
Order	Magnoliales
Family	Annonaceae
Genus	*Annona* L.
Species	*Annona squamosa*

MATERIALS AND METHOD

Study Design

This study employed a systematic literature review method to comprehensively collect, evaluate, and synthesize available scientific evidence on the phytochemistry and pharmacological activities of *Annona squamosa* L. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility.

Data Sources and Search Strategy

A comprehensive search was conducted across multiple scientific databases, including: PubMed, ScienceDirect, Scopus, Web of Science, and Google Scholar. Keywords and Boolean operators were used in combination to retrieve relevant articles: "*Annona squamosa*" OR "*sugar apple*" OR "*sweetsop"* AND (phytochemistry OR phytochemical compounds OR bioactive constituents OR pharmacology OR pharmacological activity OR medicinal uses OR traditional uses) No language restrictions were applied. However, only articles published between 2013 to 2024 were included to ensure the review reflects the most recent research progress.

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
- Original research articles, review articles, and ethnobotanical studies on *Annona squamosa*	- Studies not specifically focusing on *Annona squamosa*
- Studies reporting on phytochemical compounds, traditional uses, or pharmacological activities	- Articles lacking primary data (e.g., abstracts only, conference proceedings)
- Publications in peer-reviewed journals	- Non-scientific reports, blogs, or anecdotal evidence

Data Extraction and Management

Relevant data were extracted from the selected studies using a standardized data extraction form. The extracted information included, study title, authors, and year of publication, geographic location of the study, plant part investigated (leaves, seeds, fruits, bark, etc.), identified phytochemical compounds, pharmacological activities and mechanisms, methods used for bioactivity testing (in vitro, in vivo, in silico). Duplicate records were removed using *Mendeley Reference Manager,* and all selected articles were screened by two independent reviewers to minimize selection bias.

RESULTS AND DISCUSSION

Annona squamosa Chemical Compound

Conducted a proximate analysis of *Annona squamosa*, reporting a moisture content of 73.9%, ash content of 1.4%, and total carbohydrates comprising 23.2% of the fruit's composition. Additionally, they found total soluble sugars at 16.6%, reducing sugars at 7.8%, fiber content of 3.3%, protein content of 1.9%, phenolic content at 0.3%, titratable acidity at 0.22%, ascorbic acid content of 31.5%, and seed oil content at 25.5%. In another study, analyzed the chemical profile of Brazilian *A. squamosa* fruit pulp and found that sugars constituted 58% of the dry mass [10]. Their study also identified a low concentration of triglycerides and a notable presence of the diterpenoid compound kaur-16-en-18-oic acid at 0.25% in the lipid fraction. Furthermore, their analysis of the fruit pulp's essential oil revealed α-pinene (25.3%), sabinene (22.7%), and limonene (10.1%) as the predominant components [11].

Comprehensive phytochemical investigations of various parts of *Annona squamosa* have revealed the presence of diverse bioactive compounds, including diterpenes (DITs), alkaloids (ALKs), annonaceous acetogenins (ACGs), cyclopeptides (CPs), and essential oils. The primary chemical structures of these constituents are illustrated in Figures 2–5. Up until February 2016, researchers have successfully isolated 33 diterpenes, 19 alkaloids, 88 acetogenins, and 13 cyclopeptides from this species [4].

1. Diterpenes

Diterpenes are a prominent class of secondary metabolites found extensively in various parts of *Annona squamosa*, such as the bark, fruit pulp, and stems, although they are notably absent in the seeds and leaves. To date, research has successfully isolated 34 distinct diterpenes from *A. squamosa* , with the majority classified under the ent-kaurane diterpene group. Ent-kaurane diterpenes are characterized by their tetracyclic diterpenoid skeleton, which is biosynthetically derived from geranylgeranyl pyrophosphate (GGPP) through the kaurene pathway. These compounds are widely recognized for their diverse biological activities, particularly their cytotoxic and anticancer properties. Phytochemical studies have shown that diterpenes extracted from the bark of *A. squamosa* exhibit potent antitumor effects, demonstrating significant cytotoxicity against various cancer cell lines, including lung and ovarian cancer cells. The mechanism underlying these activities involves the induction of apoptosis and inhibition of cell proliferation, making diterpenes promising candidates for anticancer drug development. Furthermore, the structural diversity of diterpenes contributes to their ability to interact with multiple molecular targets, enhancing their pharmacological relevance in oncology [12].

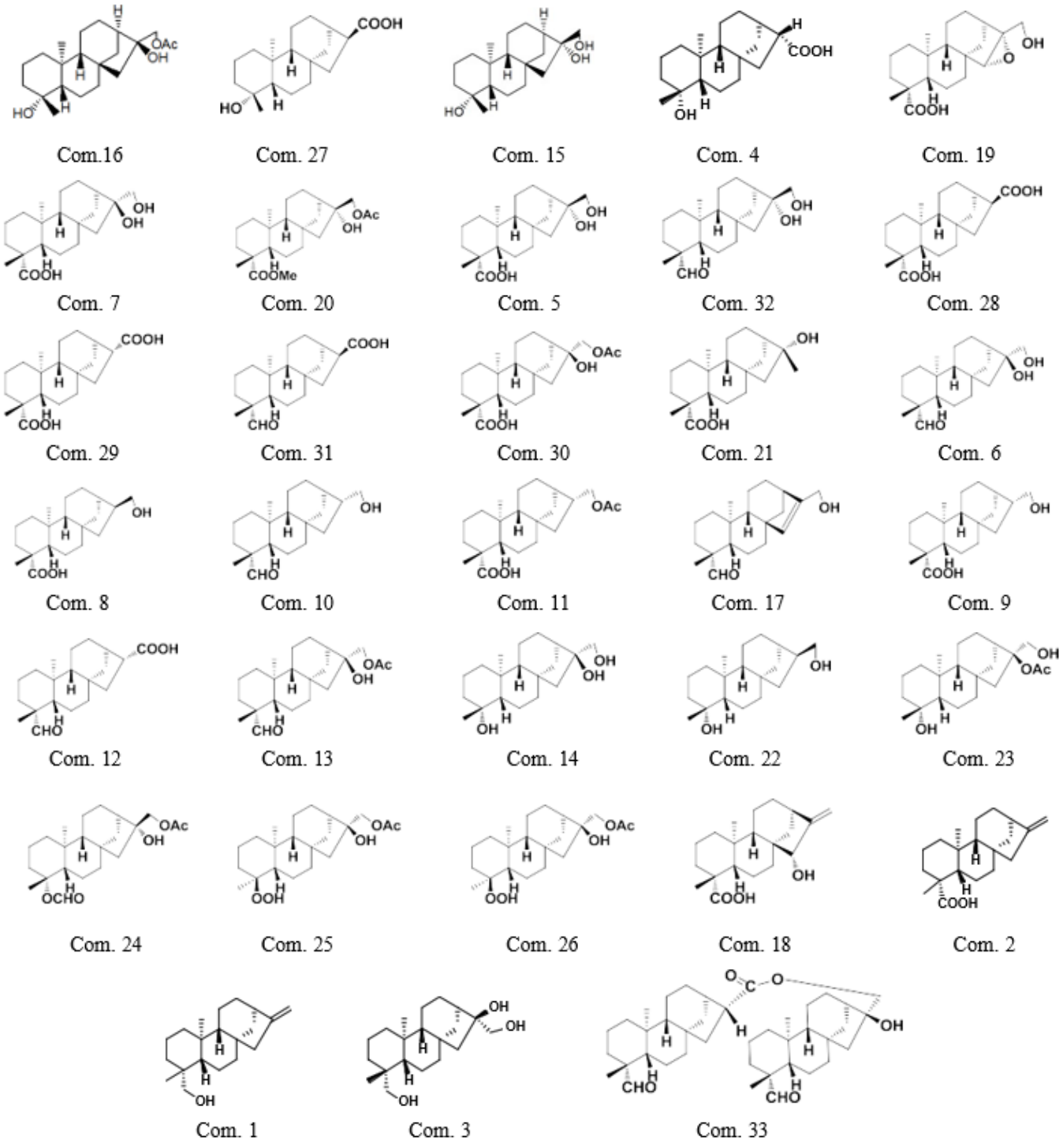

Fig. 1. Chemical structures of diterpenoids isolated from *A. squamosa* . [12].

2. Alkaloids

Alkaloids represent some of the earliest identified phytochemicals from *A. squamosa* . To date, 19 alkaloids (**Fig. 2**) have been isolated, predominantly of the aporphine type, primarily sourced from the leaves and stems. These alkaloids are recognized for their pharmacological properties, exhibiting antihypertensive, antispasmodic, antihistaminic, and bronchodilatory effects [13].

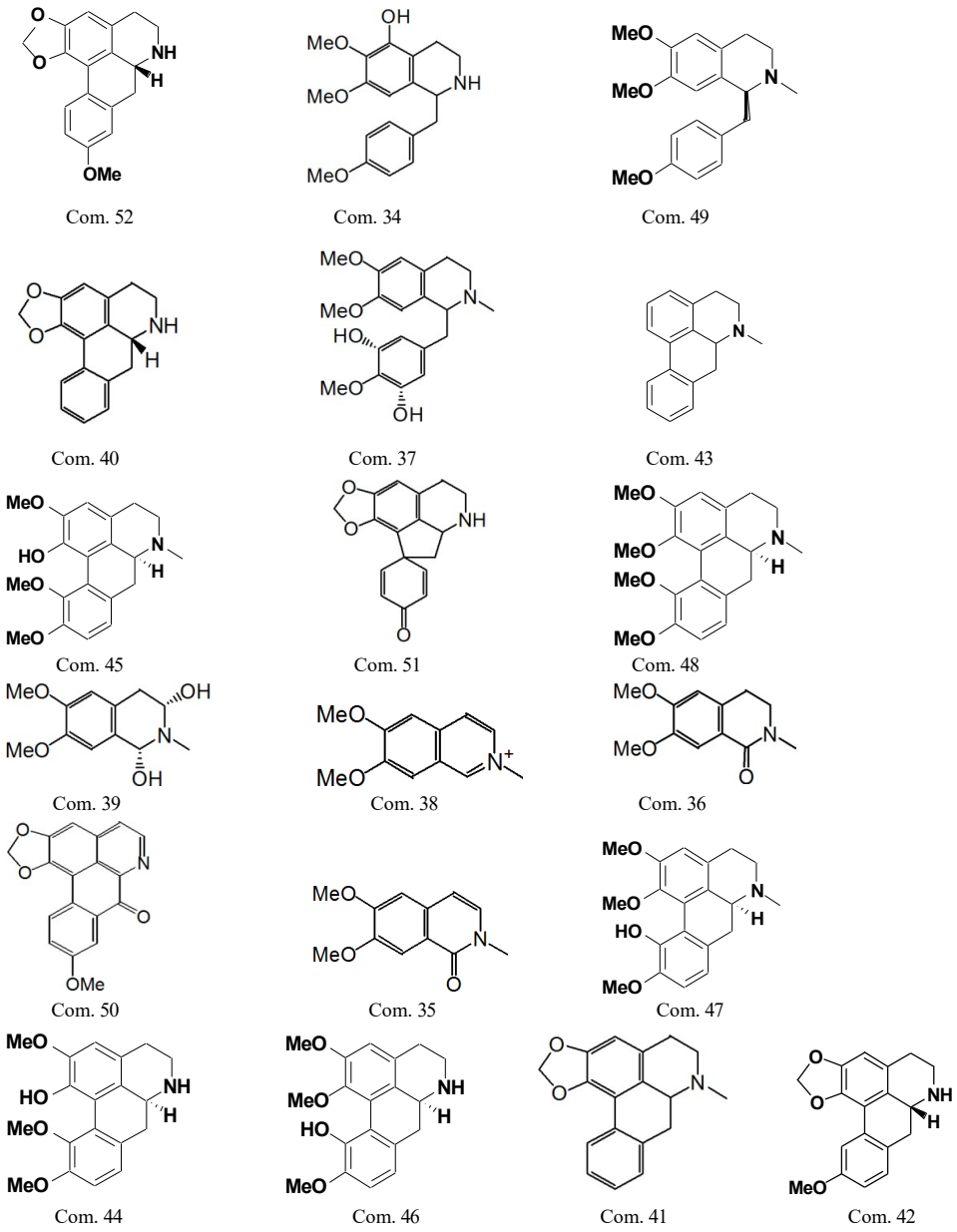

Fig. 2. Chemical structures of ALKs isolated from *A. squamosa* .

Ethnopharmacology

All parts of the *Annona squamosa* tree, much like other species within the same genus, have been traditionally used in ethnomedicine to treat a wide range of health conditions, particularly cancer and parasitic infections [14]. In Ayurveda, the fruit known as srikayas is regarded as a potent tonic. It is believed to enrich the blood, enhance muscle strength, act as an expectorant, and help soothe sensations of heat and biliousness. Additionally, srikayas have calming effects on the heart and can reduce nausea and vomiting [15]. According to Yunani medicine, the seeds are considered abortifacient and effective in removing lice from the hair. The seeds also produce oil and resin, which possess cleansing properties; when mixed with gram flour, they serve as a traditional hair wash [14]. In southern China, seed extracts have been used in folk remedies to treat malignant sores, which are understood to be cancerous lesions [16]. However, the seeds are also known to be strong irritants to the eye's conjunctiva, capable of causing ulcers. Interestingly, several studies from our laboratory have successfully used seed preparations to treat corneal injuries. The leaves of *A. squamosa* are commonly applied as a poultice to heal boils and ulcers, and their infusion is effective

in treating prolapse in children. A paste made from crushed leaves mixed with salt is traditionally applied to extract guinea-worms [17]. In Cuban traditional medicine, leaves are used to reduce uric acid levels, while leaves, bark, and unripe fruit have been employed to manage diarrhea and dysentery [13]. Beyond these uses, folkloric records highlight *A. squamosa* for its insecticidal, anticancer, antidiabetic, antioxidant, antilipidemic, and anti-inflammatory properties, many of which have been validated by modern scientific research.

Bioactivity of A. squamosa

1. Anticancer Activity

Numerous studies on extracts from various parts of this plant and isolated acetogenins (ACGs) have demonstrated strong antiproliferative effects against multiple cancer cell lines. However, only a few have explored the detailed mechanisms behind their anticancer effects. Recently, our team conducted in vivo metabolic research on the total ACGs extracted from seeds to understand their action against hepatic cancer cells (H22). These compounds induced apoptosis via the mitochondrial pathway. Complementary in vitro studies revealed that Annosquacin B, an ACG isolated from the seeds, inhibited the growth of multidrug-resistant MCF-7 cells by causing cell cycle arrest at the G1 phase [20]. Detailed findings from these studies will be published soon. Structure-activity relationship analyses of ACGs against various cancer and drug-resistant cancer cells confirmed that different ACG types exhibit varying degrees of inhibitory effects [18-19].

In a recent investigation on *A. squamosa* extracts against S180 tumor-bearing mice, it was found that the seeds likely contain the primary antitumor and toxic compounds [21]. Both aqueous and organic seed extracts induced apoptosis in a rat histiocyte tumor cell line (AK-5) by increasing caspase-3 activity, downregulating anti-apoptotic genes Bcl-2 and BclXL, and promoting intracellular reactive oxygen species (ROS) generation. DNA fragmentation and annexin-V staining further confirmed that apoptosis was triggered through oxidative stress (Pardhasaradhi et al., 2004). Additional in vitro experiments showed that these extracts caused apoptosis in MCF-7 and K-562 cells, indicated by nuclear condensation, DNA fragmentation, ROS induction, decreased glutathione levels, Bcl-2 downregulation, and PS externalization [22]. Notably, seed extracts at a dose of 18 mg/kg inhibited H22 hepatoma cell growth in mice by 69.55%, without observable side effects [24].

Assessed the anticancer effects of aqueous and ethyl acetate extracts of *A. squamosa* leaves on various cancer cell lines using MTT assays [25]. The ethyl acetate extract showed significant activity against human epidermoid carcinoma (KB-3-1) and colon cancer (HCT-116) cells, with IC50 values of 13.66 ± 0.73 μg/mL and 1.37 ± 0.64 μg/mL, respectively. Beyond in vitro and in vivo studies, clinical treatment of 86 non-small cell lung cancer patients with “Bujing Jiedu” (a formulation containing Cordyceps sinensis and *A. squamosa* seeds) showed survival rates comparable to chemotherapy. However, patients receiving this herbal treatment reported a better quality of life [26-27].

2. Antidiabetic and Hypolipidemic Activity

Diabetes mellitus is a widespread chronic disease globally, and effective traditional plant-based therapies could help reduce its complications and improve patient quality of life. Owing to the traditional use of *A. squamosa* against diabetes, several in vivo studies were conducted. Found that daily oral administration of 250 mg/kg alcoholic leaf extract to streptozotocin (STZ)-induced diabetic rats for 12 days significantly lowered fasting plasma glucose from 186.75 mg/dL to 121.04 mg/dL [28]. Similarly, aqueous extract treatment reduced glucose from 175.20 mg/dL to 94.11 mg/dL and decreased liver glycogen and pancreatic TBARS levels [29]. Additional studies confirmed the aqueous leaf extract’s antidiabetic effect in STZ-induced diabetic rats [30], which was attributed to antioxidant, hypoglycemic properties and pancreatic β-cell protection [31]. Diabetic

wounds, often chronic and slow to heal, were positively affected by the ethanolic extract of *A. squamosa* , which enhanced epithelialization and wound contraction, alongside glycosaminoglycan and collagen formation during healing [32].

3. Antioxidant Activity

Excessive intracellular reactive oxygen species (ROS) can lead to oxidative stress, metabolic dysfunction, and cell death. Natural antioxidants are thus highly valued in pharmaceuticals for mitigating ROS damage [35]. The ethanolic extract of *A. squamosa* leaves showed strong antioxidant activity via ABTS, DPPH, and nitric oxide radical scavenging, along with moderate superoxide scavenging and anti-lipid peroxidation effects [34]. Extracts from various plant parts demonstrated significant antioxidant capacity [35]. with methanol, chloroform, and aqueous leaf extracts exhibiting free radical scavenging and reducing power [36]. Wine made from *A. squamosa* fruits also showed notable antioxidant properties [37]. Several antioxidant phytochemicals have been isolated from the plant, confirming its potential as a natural antioxidant source [34].

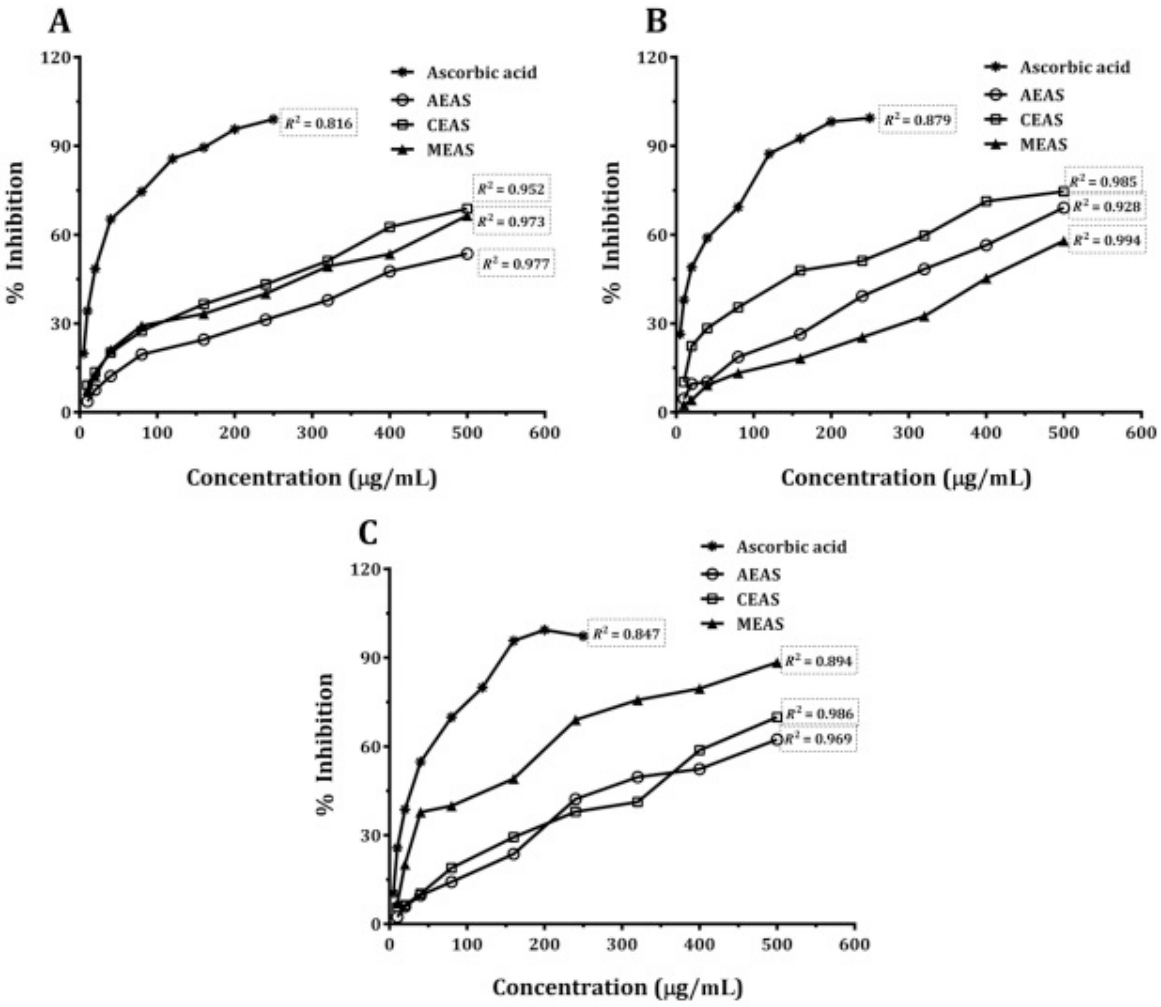

Fig. 3. Radical scavenging activity [56].

The figure illustrates a detailed comparative analysis of the antioxidant activity of three different extracts of *Annona squamosa*—namely AEAS (aqueous extract), CEAS (chloroform extract), and MEAS (methanolic extract)—against ascorbic acid, a well-known standard antioxidant. Each of the three subfigures (A, B, and C) represents separate antioxidant assays, most likely involving different reactive species or mechanisms (such as DPPH, ABTS, or FRAP), with the percentage of inhibition

plotted on the Y-axis and extract concentration (µg/mL) on the X-axis. These plots are designed to assess the dose-dependent antioxidant efficacy of the extracts by evaluating their capacity to inhibit free radicals or oxidative agents [55].

In the first graph (A), all the test samples—including the standard—show a positive correlation between concentration and % inhibition, indicating that higher concentrations lead to greater antioxidant activity. Ascorbic acid demonstrates the steepest curve, reaching nearly 100% inhibition at 500 µg/mL, confirming its potent free radical scavenging ability. The regression value for ascorbic acid is R2=0.8166R^2 = 0.8166R2=0.8166, suggesting a moderately good fit to the dose-response model. Among the *Annona squamosa* extracts, MEAS displays the most pronounced antioxidant activity with the highest R2=0.9777R^2 = 0.9777R2=0.9777, followed by CEAS (R2=0.9733R^2 = 0.9733R2=0.9733) and AEAS (R2=0.952R^2 = 0.952R2=0.952). This trend indicates that the methanolic extract possesses more potent and consistent antioxidant properties compared to aqueous and chloroform extracts, likely due to better solubility and extraction efficiency of phenolic and flavonoid compounds in methanol [55].

In the second graph (B), the overall inhibition percentages are slightly higher across the same concentration range. Ascorbic acid again outperforms the extracts, with an improved regression coefficient (R2=0.8799R^2 = 0.8799R2=0.8799), suggesting more linearity in its dose-response behavior in this assay. MEAS continues to show superior inhibition, achieving an almost linear response (R2=0.994R^2 = 0.994R2=0.994), followed by AEAS (R2=0.985R2 = 0.985R2=0.985) and CEAS (R2=0.928R^2 = 0.928R2=0.928). These results reinforce the pattern seen in Panel A and further support the antioxidant dominance of the methanolic extract, possibly due to its richer phytochemical profile, including polyphenols, alkaloids, and saponins known for free-radical scavenging [55].

The third graph (C) maintains a similar upward trend, with ascorbic acid showing a sharp increase in inhibition at lower concentrations and reaching maximum activity at higher doses (R2=0.847R^2 = 0.847R2=0.847). Notably, CEAS shows a significant improvement in antioxidant performance in this assay, leading the three extracts with an R2=0.986R^2 = 0.986R2=0.986. MEAS follows closely (R2=0.969R^2 = 0.969R2=0.969), and AEAS trails with R2=0.894R^2 = 0.894R2=0.894. This shift in extract performance suggests that different phytochemical classes present in the chloroform extract may be more effective in the specific oxidative system used in this assay. It highlights the complexity of antioxidant activity, which is not only dependent on total phenolic content but also on the mechanism of action of the assay and the specific bioactive compounds present [55].

Collectively, these three panels consistently demonstrate that the antioxidant activity of *Annona squamosa* extracts is dose-dependent, with increasing concentration resulting in higher % inhibition. As expected, ascorbic acid consistently shows the highest antioxidant activity, confirming the validity of the assays. Among the plant extracts, MEAS (methanolic extract) generally exhibits the strongest and most consistent antioxidant performance across different assays, likely due to its ability to extract a wider range of polar antioxidant compounds. However, CEAS (chloroform extract) also displays notable activity in certain contexts, suggesting that non-polar bioactives (such as terpenoids or certain alkaloids) may also contribute to antioxidant properties. The strong linearity in regression coefficients (all R2>0.89R^2 > 0.89R2>0.89) across the extracts further confirms the reliability of the data and supports the pharmacological relevance of *A. squamosa* in oxidative stress-related applications. This detailed analysis highlights not only the antioxidant potential of *Annona squamosa* but also emphasizes the importance of solvent polarity and assay type in influencing the observed bioactivity. Such findings support the plant's ethnomedicinal use and provide a scientific foundation for its application in natural antioxidant formulations.

4. Anti-inflammatory and Analgesic Activity

Inflammation and pain are common defense responses to injury and important clinical symptoms [38]. Many medicinal plants, including *A. squamosa* , have proven effective against pain and inflammation. Intraperitoneal administration of ethanolic leaf extract (100 mg/kg) in rats reduced carrageenan-induced paw edema by 47.16%, demonstrating anti-inflammatory properties [38]. Oral administration of petroleum ether bark extract showed even stronger inhibition at lower doses [39]. Both extracts also significantly reduced acetic acid-induced abdominal writhing and thermal pain responses, indicating strong antinociceptive effects [40]. Several isolated phytochemicals from *A. squamosa* suppressed inflammatory cytokines TNF-α and IL-6 [39]. Additionally, aqueous leaf extract (300 mg/kg for 4 weeks) counteracted acetic acid-induced ulcerative colitis, decreasing levels of CAT, GSH, and Gpx, showing antiulcerative potential [42].

5. Antihypertensive Activity

Certain alkaloid fractions isolated from the sugar apple (Annona squamosa) have been shown to possess antihypertensive effects, meaning they can help lower high blood pressure. An early study by Husain (1992) demonstrated the potential of these alkaloid compounds in managing hypertension [43]. Further research by Morita et al. (2006) revealed that seed extracts from sugar apple induce vasorelaxation, or the relaxation and widening of blood vessels, specifically in the rat aorta. This vasorelaxation is significant because dilated blood vessels reduce vascular resistance, thereby lowering blood pressure. From these extracts, a cyclic peptide named cyclosquamosin B was identified as the active compound responsible for the hypotensive effect [41]. The likely mechanism of action of cyclosquamosin B involves the inhibition of voltage-dependent calcium (Ca^{2+}) channels in peripheral smooth muscle cells. By blocking these calcium channels, the influx of Ca^{2+} ions into smooth muscle cells is reduced, leading to decreased muscle contraction and resulting in vessel relaxation or dilation. This mechanism explains how sugar apple seed extracts and cyclosquamosin B can exert a significant antihypertensive effect [44].

6. Hepatoprotective Activity

Medicinal plants have long been recognized for their potential to provide effective and safer alternatives in the treatment of liver toxicity. In particular, an in vivo study conducted by [45] demonstrated that the alcoholic leaf extract of *Annona squamosa* significantly attenuated liver injury induced by diethylnitrosamine (DEN) in mice. This protective effect was evidenced by the normalization of elevated bilirubin levels, an important marker of liver dysfunction, as well as improvements in liver histology, indicating restoration of normal liver tissue architecture. Similarly, research by [46] showed that both alcoholic and aqueous extracts of *A. squamosa* were able to reduce liver toxicity caused by the anti-tuberculosis drugs isoniazid and rifampicin. However, while these extracts mitigated liver damage, they did not completely reverse it, suggesting that *A. squamosa* extracts may be more effective as complementary or adjunctive therapies rather than standalone treatments in managing drug-induced hepatotoxicity. These findings highlight the therapeutic potential of *A. squamosa* in protecting liver health, warranting further investigation into its mechanisms and clinical applications [47].

7. Antiparasitic Activity

Protozoal infections like leishmaniasis, sleeping sickness, Chagas disease, and malaria affect millions globally (Glaser and Holzgrabe, 2016). Resistance, toxicity, and side effects limit current treatments [48]. Natural extracts like *A. squamosa* offer safer alternatives. Essential oils from *A. squamosa* showed inhibitory activity against Trypanosoma cruzi with IC50 values under 15 µg/mL [49]. Lower antiprotozoal effects were reported from pericarp extracts against various parasites [50]. Bioassay-guided

isolation of ACGs from seeds showed significant activity against nematodes [51]. Alkaloids and ACGs from leaves were active against Leishmania chagasi promastigotes and amastigotes with IC50 values ranging from 13.5 to 37.6 µg/mL [52].

8. Antimalarial Activity

Malaria remains a major health challenge, particularly in Africa, with drug resistance complicating treatment [53]. The methanolic leaf extract of *A. squamosa* exhibited promising antimalarial activity against chloroquine-sensitive (3D7) and resistant (Dd2) strains of Plasmodium falciparum, with IC50 values of 2 µg/mL and 30 µg/mL, respectively. Bark extracts were less potent [55]. Further studies confirmed activity against both sensitive and resistant strains, isolating three alkaloids with IC50 values from 7.8 to 34.2 µM [54].

CONCLUSION

Annona squamosa is a rich source of diverse bioactive chemical compounds, including diterpenes, alkaloids, acetogenins, cyclopeptides, and essential oils, with significant variations in their distribution across plant parts. These compounds contribute to the plant's broad pharmacological potential demonstrated through extensive ethnopharmacological uses and scientific validation. Notably, diterpenes exhibit potent anticancer activity by inducing apoptosis and inhibiting tumor growth. Extracts and isolated compounds from *A. squamosa* also show promising anticancer effects against various cancer cell lines and in animal models, with mechanisms involving oxidative stress and apoptotic pathways. Beyond anticancer properties, *A. squamosa* demonstrates beneficial effects in managing diabetes by lowering blood glucose levels and protecting pancreatic function. Its antioxidant activity helps mitigate oxidative stress, while anti-inflammatory and analgesic properties have been confirmed through in vivo studies. Alkaloid fractions and cyclic peptides from seeds contribute to antihypertensive effects by promoting vasorelaxation via calcium channel inhibition. Hepatoprotective activity is evident in reducing chemically induced liver damage, highlighting its potential as an adjunctive therapy. Furthermore, *A. squamosa* exhibits antiparasitic and antimalarial activities, showing effectiveness against protozoal parasites such as Trypanosoma and Plasmodium species, which are major global health concerns. These multifaceted bioactivities support the traditional ethnomedicinal applications of *A. squamosa* and encourage further research into its clinical potential for treating cancer, diabetes, hypertension, liver disorders, parasitic infections, and inflammation.

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