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Chemodiversity of *Annona Squamosa* Secondary Metabolites

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ABSTRACT

Annona squamosa a member of the Annonaceae family is an important fruit cultivated in Egypt, Bermuda, Brazil, India, Mexico, South and Central America, considered a notable source of secondary metabolites with a broad range of biological activities including antimicrobial, antiprotozoal, anticancer, antidiabetic and antioxidant activity. The sugar apple fruit is prized for both its full nutritional profile and edible flavor. It is a great source of several vital nutrients, such as antioxidants, potassium, magnesium, iron, vitamins (including C, B6, and riboflavin), and dietary fibers. This study aims to incorporate existing data on *A. squamosa's* phytochemicals, traditional applications, and bioactivities based on several studies, with the ultimate goal of advancing knowledge of the plant's potential medical benefits.

KEYWORDS: *Annona squamosa*, Antimicrobial, Anticancer, Antioxidant.

1. INTRODUCTION

Apart from their essential role in photosynthesis, plants may also be suppliers of natural products. Since the beginning of medicine, people have utilized natural products to maintain their health. The bioactive compounds and phytochemicals present in plants have significantly facilitated the discovery and development of new drugs over the past century. There is a lot of interest in the bioactivities of substances because of the importance of plant bioactive chemicals in health [1].

Among these plants, *Annona squamosa*, having several anonyms including sugar apple, sweet sop, custard apple, and sitaphal, A.squamosa belongs to the Annonaceae family, which has about 2300 species and 135 genera [2]. The birthplace of *A. squamosa* is not clear. It is a semi-deciduous tree widely distributed in tropical South America and in the West Indies. The Spaniards probably carried seeds from the New World to the Philippines and the Portuguese were assumed to introduce the sugar apple to southern India before 1590, nowadays, it is cultivated in tropical and sub-tropical regions worldwide [3]. Researchers have discovered, isolated, and identified a wide range of secondary metabolites from various parts of *A. squamosa*, including acetogenins, flavonoids, alkaloids, and essential oils [4]. The entire *A. squamosa* tree, like other species in the same genus, is extensively used in traditional medicine to treat a variety of illnesses and human diseases, particularly cancer [5]. The species belonging to the Annona genera are known to elicit many biological activities, including those that are antitumor, anti-inflammatory, antioxidant, antinociceptive, antiprotozoal, antipyretic, antiulcer, antihyperglycemic, anthelmintic, antileishmanial, antimalarial, antifungal, and antimicrobial. These activities are supported by whole extracts, fractions, or pure compounds

[6]. Seed extraction was a traditional treatment for "malignant sores," or cancer, in the southern part of China The plant's stem, roots, twigs, fruit, seeds, bark, and leaves have been traditionally utilized for numerous purposes. Various preparation procedures, including as pastes, infusions, and decoctions, have been described. [7]. We have outlined the phytochemicals and bioactivities of *A. squamosa* in this review.

2. METHODS

The preparation of this study involved a thorough evaluation of the literature that was accessible through the use of major scientific databases: PubMed,Scopus, and Google Scholar. *Annona squamosa*, *Annona squamosa*'s traditional applications, and *Annona squamosa*'s phytochemistry are the keywords utilized to gather about 34 published papers collected over 3 weeks. Following the compilation of published articles, the findings underwent analysis and were categorized based on the review's subject.

3. DISCUSSION

3.1. Phytochemical Studies on *A. Squamosa*

Comprehensive analyses of the phytochemical composition of several parts of A.squamosa revealed the presence of a variety of phytochemicals and components. Alkaloids (Table no. 1), flavonoids (Table no. 2), acetogenins (Table no. 3), terpenes (Table no. 4) and Enta-Kaurane diterpenes (Table no.5) are the general categories into which the phytochemical profile of *A. squamosa* may be divided having many biological activities. [8].

3.2. Biological Activities of Genus *Annona* and *A. Squamosa*

3.2.1. Ethnomedicinal uses of Genus *Anonna*

The leaves of *A. squamosa* are crushed, applied to wounds and ulcers, and smelled to treat hysteria and fainting episodes in India. In tropical America, decocted leaves are used as a tonic, febrifuge, and cold treatment in addition to being used systemically to treat dysentery (India). In El Salvador, unripe fruit was used to cure diarrhea, whereas crushed ripe fruit was applied to surface malignancies (India), diarrhea and dysentery were treated with the stem bark and root [9]. Annona muricata (soursop) has been utilized in Togo's traditional medicine to treat hypertension and diabetes [10], the leaves also have been used as an aphrodisiac and a therapy for boils and spasms in Indonesian traditional medicine [9].

3.2.2. Antiprotozoal Activities

According to ethnopharmacological research, *A. squamosa* was recommended for the treatment of malaria. Subsequent investigations demonstrated that *A. squamosa* seed extract was abundant in flavonoids and alkaloids. The crude methanolic extract of *A. squamosa* demonstrated mild activity with an IC50 value of 30 µg/mL against Plasmodium falciparum 3D7 , in contrast to IC50 = of 0.021µg/mL obtained from chloroquine control [11].

3.2.3. Antibacterial Activities

The rise of multidrug resistance in various organisms and the adverse effects of synthetic antibiotics have prompted the exploration of plant-derived antimicrobial medicines to manage microbial diseases. All the unique components of the plant exhibited sensitivity to many organisms. The leaves of *A. squamosa* are used in traditional medicine for the treatment

and prevention of diseases, and recent studies have demonstrated its antibacterial properties [12]. It has been found that extracts from the seeds of *A. squamosa* have antimicrobial properties. The oil derived from *A. squamosa* showed high sensitivity to *Bacillus subtilis* and *Staphylococcus aureus* [13]. The bark of *A. squamosa* also has antibacterial activity. *Bacillus coagulans* and *Escherichia coli* exhibit greater susceptibility to the methanol extract of stem bark compared to other bacterial strains. The ability of *A. squamosa* leaf extracts to interfere with cell wall production is responsible for their antibacterial action. *B. cereus*'s altered morphology after exposure to inhibitory doses of *A. squamosa* extract provides compelling evidence for the plant's role in cell wall rupture [12].

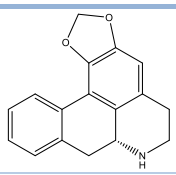
3.2.4. Anticancer Activities:

Cancer has become one of the most prevalent causes of mortality for several decades. Multiple factors, including unregulated cellular division and metastasis, cause it. Each year, over 7.6 million individuals succumb to cancer, with the number projected to rise to around 13.1 million by the year 2030 [14]. Naturally occurring bioactive substances that cause apoptosis have attracted a lot of attention in the field of anticancer drugs in recent years. Apart from the aforementioned antibacterial properties, *Annona* plant crude extracts and specific alkaloids have demonstrated strong anticancer and antitumor properties [9]. Roemerine isolated from custard apple enhanced the response that vinblastine (ED_{50} > 20 µg/mL) elicited against MDR KB-V1 or KB-3 cells. he alkaloid isocoreximine isolated from *Annona cherimola*, at concentration of 50 µg/mL indicated cytotoxicity against K-562, U-251, PC-3, HCT-15, and MCF-7 with % inhibition of cell viability 94.15%, 65.23%, 78.71%, 63.05%, and 85.76%, respectively. Isocoreximine showed *in vitro* cytotoxic activity against K-562, U-251, PC-3, HCT-15, and MCF-7 with % of inhibition of cell viability 94.15%, 65.23%, 78.71%, 63.05%, and 85.76%, respectively [9].

3.2.5. Antioxidant Activities

Numerous investigations have demonstrated the importance of *A. squamosa* antioxidant components in reducing the harmful effects of free radicals [15]. Numerous investigations were carried out to ascertain the antioxidant capacity of the *A. squamosa* extracts. The moderate antioxidant activity of extracts in acetone, methanol, and water was reported to be scavenged by DPPH with IC_{50} value = 33.9 ± 4.8 µg/mL for acetone, 51 ± 1.6 µg/mL for methanol, and 98.3 ± 0.4 µg/mL for aqueous extracts [16]. The kaempferol 3-*O*-*β*-glucoside and kaempferol *3-O-β*-diglucoside from *A. crassiflora* leaves might inhibit the occurrence of edema. Doses of 100 mg/kg and 300 mg/kg can inhibit the formation of carrageenan-induced edema to about 53% and 47%. The essential oil from the leaves of A. sylvaticaat doses of 20 mg/kg and 200 mg/kg showed 19% and 27% inhibition .These results can be used in the development of herbal anti-inflammatory medicine [3]. The attached tables include isolated compounds from different chemical classes with their biological activities.

Table 8: Alkaloids reported from *A. Squamosa*

Compound Name	Chemical Structure	Biological Activity	Reference
Anonaine		antibacterial, antifungal, antioxidation, anticancer, antidepression, and vasorelaxant activity.	[3,17]

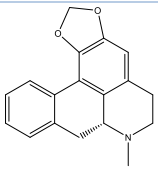
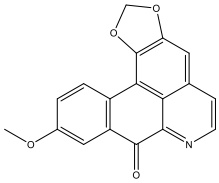
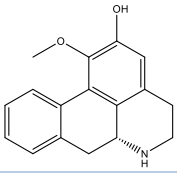
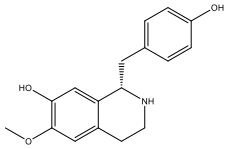
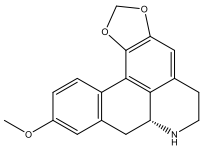
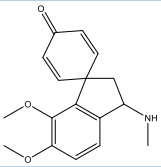
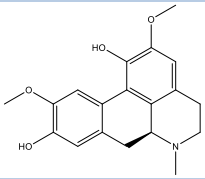
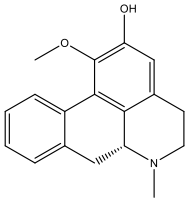
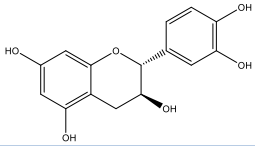
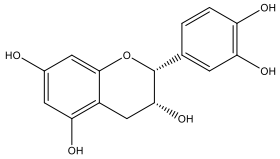
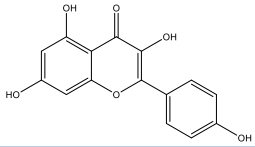
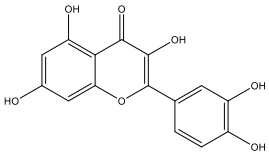
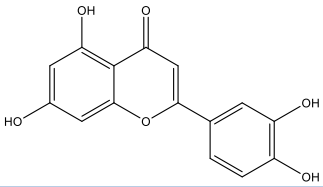
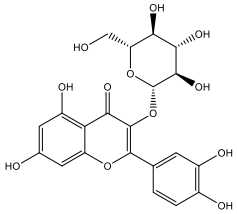
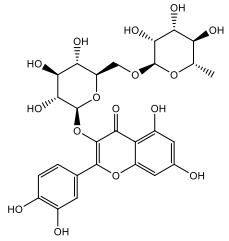
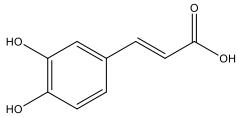
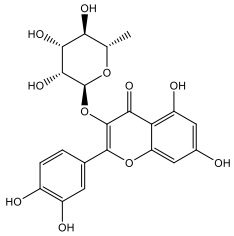
Roemerine		exhibit potential antibacterial action against *Salmonella typhimurium*, *Bacillus subtilis*, and *Escherichia coli.*	[3,18]
Lanuginosine		Immune stimulating activity	[3,19]
Asimilobine		Exhibited anti-leishmanial biological activity with IC_{50} values = 29.8 ± 1.5µM & 50.0 ± 4.0µM, respectively. Also exhibited anti-fungal activity with an IC_{50} = 16.0µg/mL	[9,20]
Coclaurine		Topoisomerase II activity inhibition with IC_{50}=133.53µM.	[21,22]
Xylopine		has cytotoxic activity to cancer cells.	[23]
Stepharine		Cytotoxic activity against 2 human lung cancer cell lines, weak antifungal potential.	[4,24]
Isoboldine		Leishmanicidal activity against the promastigotes of *L. mexicana.*	[25,26]
Nornuciferine		Anti-hyperuricemic, Anti-hyperlipidemia and anti-inflammatory effects.	[4,25,27]

Table 9: Flavonoids reported from *A. Squamosa*

Compound Name	Chemical Structure	Biological Activity	Reference

Catechin		Antidiabetic, anticancer, anti-obesity, neuroprotective and hepatoprotective.	[28,29]
Epicatechin		Antidiabetic, anticancer, anti-obesity, neuroprotective and hepatoprotective.	[28,29]
Kaemferol		Anticancer activity in cancer cells from different organs including breast, lung, gastric, ovarian, and blood cancers	[28,30]
Quercetin		Anti-inflammatory, antihypertensive and anti-obesity effects	[28,31]
Luteolin		Has potent anti-inflammatory and antioxidant properties	[28,32]
Isoquercetin		Exhibit antioxidant, anti-inflammatory, and anticoagulant activities.	[28,33]
Rutin		antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective and cardioprotective activities	[4,34]
Caffeic acid		Antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective and cardioprotective activities	[35,36]
Quercetin-3-O-rhamnoside		Cytotoxic, phytotoxic, antimicrobial and antioxidant effects	[37,38]

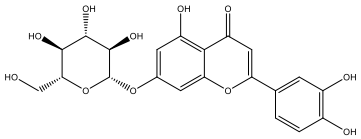
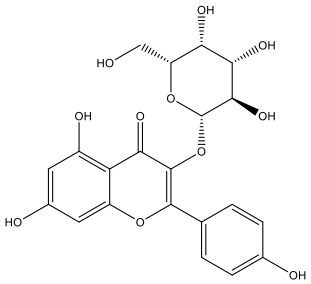
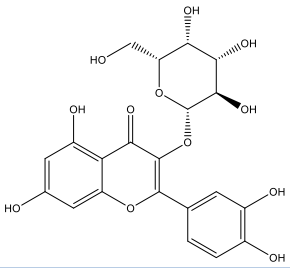
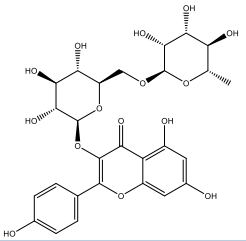
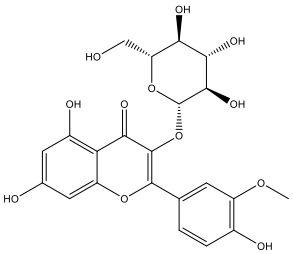
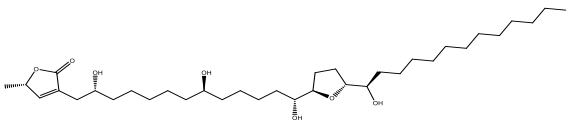
Luteolin-7-O-glucoside		Shows suppression of oxidative stress & inflammatory mechanisms.	[37,39]
kaempferol-3-O-galactoside		Exhibit anticarcinogenic, anti-inflammatory, antibacterial, antifungal, and antiprotozoal activities.	[37,40]
Hyperin		anti-inflammatory, antithrombotic, antidiabetic, hepatoprotective, and antioxidant effects	[28,41]
Nicotiflorin		Anti-inflammatory, antioxidant, antibacterial, antiviral, analgesic, and neuroprotective effects.	[4,42]
Isorhamnetin-3-O-glucoside		Antioxidant, anticancer, antimicrobial, antiviral, anti-inflammatory and anti-diabetic effects	[37,43]

Table 10: Acetogenins reported from *A. Squamosa*.

Compound Name	Chemical Structure	Biological Activity	Reference
Annonacin		Exhibited antiproliferative activity on EC cell lines (ECC-1: Endometrial cancer cell-1 and HEC-1A: Human endometrial carcinoma-1A) with EC_{50} values	[28]

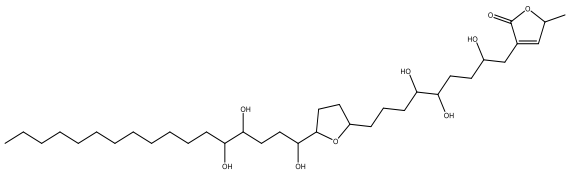
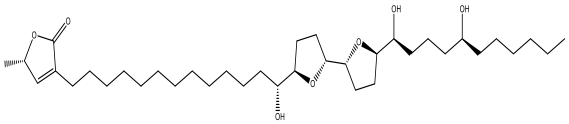
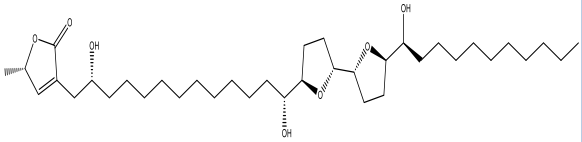
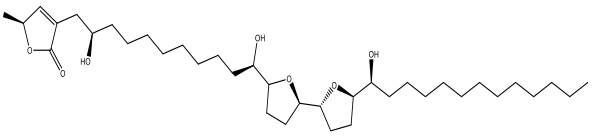
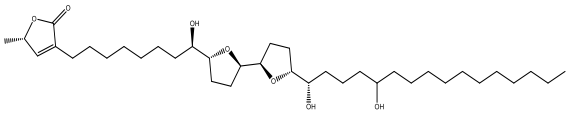
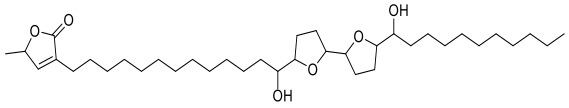
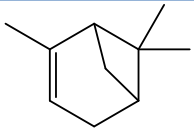
		from 4.62 to 4.92µg/mL.	
Murihexocin C		Toxic activity against human colon carcinoma (Col 2).	[3,44]
Squamocin		have antitumor, immunosuppressive, antiprotozoal, anthelmintic, and antimicrobial properties.	[28,45]
Bullatacin		Toxicity against breast MDR MCF-7/Adr, hepatoma H22, and leukemia L1210 cancer cells	[3,28]
Squamotacin		Toxicity against breast (MDR MCF-7/A) cancer cells	[3]
Annosquacin I		Toxicity against breast MCF-7, lung A549 and liver HepG2 cancer cells	[46]
Squamocin L		Toxicity against leukemia L1210 cells	[3]

Table 11: Terpenes reported from *A. Squamosa*.

Compound Name	Chemical Structure	Biological Activity	Reference
α-pinene		Antimicrobial, apoptotic, antimetastatic, and antibiotic properties. Suppression of MAPKs and the NF-κB pathway	[47–49]

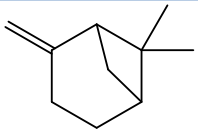
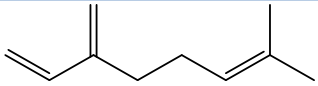
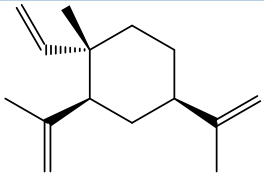
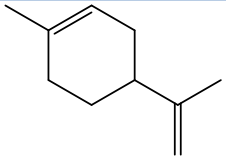
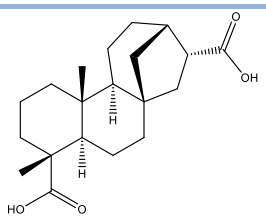
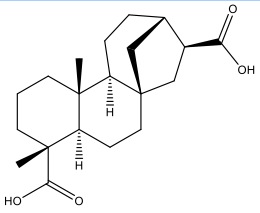
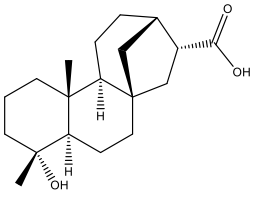
β-Pinene		Antibacterial, antidepressant, cytotoxic, and antimicrobial.	[48–50]
Myrcene		Anxiolytic, antioxidant, anti-inflammatory, analgesic properties	[49,51]
β-elemene		Regulates inflammatory factors (TNF-*α*, IFN, TGF-*β*, and IL-6/10) and oxidative stress *in vivo* and *in vitro*	[49,52]
Limonene		Antimicrobial susceptibility and mechanism against *Listeria monocytogenes*	[49,53]

Table 12: Enta-Kaurane diterpenes reported from *A. squamosa*.

Compound Name	Chemical Structure	Biological Activity	Reference
16*α*-hydro-ent-kauran-17,19-dioic acid		Complete inhibitory effects on rabbit platelet aggregation at 200 µM	[3,54]
16*β*-hydro-ent-kauran-17,19-dioic acid		Complete inhibitory effects on rabbit platelet aggregation at 200 µM	[3,54]
4*α*-hydroxy-19-nor-ent-kauran-17-oic-acid		Complete inhibitory effects on rabbit platelet aggregation at 200 µM	[3,54]

4. CONCLUSION

Annona squamosa is an amazing fruit tree that has important nutritional and therapeutic benefits. Its fruits are edible, and its many bioactive components have potential uses in medicine. In order to fully investigate *Annona squamosa*'s potential in the medical field and to

advance sustainable farming methods that will enable its wider availability, more study is necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX A: LIST OF ABBREVIATIONS

MRSA	Methicillin-resistant Staphylococcus aureus
MDR	Multi-drug resistant
MIC	Minimum Inhibitory Concentration
ED_{50}	Effective dose for 50% of the population
DPPH	2,2-diphenyl-1-picrylhydrazyl
IC_{50}	Half-maximal inhibitory concentration