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From Seeds to Remedies: Exploring the Therapeutic Potential of Selected Medicinal Plants of *Annona* genus (*A. squamosa*, *A. reticulata*, and *A. muricata*)

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Abstract Both conventional and modern medicine rely on traditional herbs due to their medicinal effectiveness and low side effects. Some of these, like *Annona* species, are used as food because their fruits are edible, and scientists have shown that they contain many bioactive substances, such as alkaloids, peptides, lectins, acetogenins, isoquinalones, and volatile oils. These molecules emphasize their pharmacological relevance and help explain the therapeutic actions of plants. The goal of this review is to look at the medicinal potential of *Annona* species, especially *Annona squamosa, A. reticulata,* and *A. muricata*. These species have a lot of useful medical properties, such as the ability to fight diabetes, bacteria, cancer, fungi, blood vessel growth, seizures, inflammation, and blood vessel relaxation. This review combines the traditional use, phytochemical composition, and therapeutic qualities of these species using current information. Methodologies used in this review comprise a thorough analysis of scientific studies concerning the *Annona* species and present literature. Among other health advantages, the main findings show that the bioactive chemicals in these plants can help collagen and elastin synthesis, lower oxidative stress, and increase skin moisture. The main findings of this research highlight the great therapeutic value of *Annona* species, offering natural solutions for the management and treatment of many diseases. By stressing the two advantages of these plants that they satisfy demand for more efficient treatments and help to solve the growing issue of drug resistance this work improves the field. Moreover, it highlights the important part *Annona* species play in both conventional and modern medicine, therefore opening the path for the creation of fresh plant-based medicinal agents.

Keywords *Annona*, Anti-Cancer, Phytochemistry, Pharmacological Uses, Acetogenins, Seeds

1. Introduction

Herbal remedies have a long history and contain biologically active components including primary and secondary metabolites. These bioactive chemicals support health and may treat many common human diseases [1]. Many Phyto active substances have been employed as lead compounds for the creation of synthetic derivatives with pharmacological properties. These compounds can be used with current medicine to create novel medicinal compositions [2]. Various plant species are being examined for anticancer effect, and a few putative bioactive chemicals, for example vinca alkaloids, podophyllotoxins, taxols, and curcuminoids, have already been found [3].

Diverse scientific facts have demonstrated that herbal plants are safer, effective, less expensive, and more readily accessible, therefore allowing traditional medical practitioners to be in demand. As per the World Health Organization (WHO), traditional herbal remedies are utilized in about 80% of developing nations such as India, Brazil, Thailand, Japan and China [4]. Therapeutic herbs and extracts are used in 85% of these nations. Massive efforts have been undertaken to find and analyze medicinal plant extracts for novel bioactive chemicals and biological functions to create innovative formulations. Several research on the pharmacological qualities of diverse sections of these genera has been published to expand understanding of phytoconstituents, traditional uses, and reported activities of the chosen plant species' seeds [5].

Herbs play a vital part in nature because of their ability to photosynthesize; they provide a basis for various primary and secondary metabolites, polyphenols, phytosterols, fatty acids, and other chemicals that are employed in traditional medicine. Bioactive and phytoconstituents found in plants have played key roles in the invention of novel pharmaceuticals and pharmaceutical firms in recent decades [6]. Indigenous peoples have long exploited the seeds of *Annona squamosa*, *Annona reticulata*, and *A. muricata* to treat problems such as diabetes, inflammation, parasite infestations, abortifacient, insect repellent, cancer, and other ailments. Table 1 details the historic utilization of these species' seeds.

Table 1. Traditional uses of *A. squamosa, A. reticulata* and *A. muricata* seeds

Species	Activity
Annona squamosa	Abortifacient
	Hair decontaminant Pediculicidal Anthelmintic activity [28]
	Malignant sores Irritant of the conjunctiva [29]
	Anti-parasitic [14]
	Insecticide [30]
Annona reticulata	Insecticidal
	Dysentery [31]
	Epilepsy Cardiac problems Hemorrhage [10]
Annona muricata	Larvicidal [32]
	Anti-pediculicidal activity [33]
	Antibacterial activity, insecticidal [34]
	Astringent Fish-poison [17]
	Anthelmintic activity Parasitic infection Insect repellent [18]

2. Research Methodology

This review consists of research articles and reviews on *A. squamosa*, *A. reticulata*, and *A. muricata* published in 2024. The publications were accessed via Google Scholar, PubMed, Science Direct, and Scopus. The review was performed by targeting the selected seeds from the *Annona* genus, which have acetogenins as their major component.

2.1. Seeds of *Annona* Family with Pharmacological Properties

Annonaceae is a plant family with approximately 2000 species and 120 genera; it is a vast family but one of the least recognized families considering chemical contents and pharmacological activities. This genus is known to have potential pharmacological properties such as anti-diabetic, anti-microbial, anti-cancer, anti-fungal, anti-angiogenic, anti-epileptic, anti-inflammatory, and vasorelaxant effect. Among these plants are *Annona squamosa*, *Annona reticulata*, *Annona muricata*, *A. Montana*, *A. crassiflora*, and others [7].

Annona species produce annual fruits and are cultivated in many places of the globe. They are indigenous to the tropical and subtropical climates. Even though they belong to the same family they have unique morphological features and are known around the world with numerous synonyms and vernacular names. They belong to Kingdom: Plantae, Order: Magnoliids, Division: Magnoliophyta, Family: Annonaceae, and Genus: *Annona*. The specifics of the scientific classification, synonyms, common names, and vernacular names are explained in Table 2.

Table 2. Botanical Description and Distribution of *A. squamosa, A. reticulata,* and *A. muricata* [8-10]

Contents	**Plant name**		
	Annona squamosa	*Annona reticulata*	*Annona muricata*
Botanical name	*Annona squamosa Linn.*	*Annona reticulata Linn.*	*Annona muricata Linn.*
Synonyms	*Annona cinerea* *Guanabanus squamosa* *Annona asiatica* *Xylopia glabra* *Annona forskahlii* *Alphonsea forskahlii,* *Xylopia frutescens,* *Annona glabra*	*Annona excelsa* *Annona longifolia* *Annona riparia* *Annona longifolia* *Annona laevis*	*Annona crassiflora* *Guanabanas muricatus* *Annona macrocarpa* *Annona bonplandiana* *Annona clearness*
Common name	Bullock's Heart Sugar Apple Sweetsop Buah Nona Custard Apple Seri Kaya Anona Nona	Netted Custard-apple Bullock's heart Frutoda-Condessa Ramphal Corazon Ox heart custard apple	Guanabana, Durian Belanda Graviola Prickly Custard Apple Durian Makkah Durian Europa Durian Benggala
Local names	Kannada: Sitaphala Tamil: Sitapalam Telegu: Sita-phalamu Malayalam: Seethappazham Marathi: Aathachakka Hindi: sharifa	Kannada: Ramaphala Malayalan: ManilanilamTelegu: Ramasitapalam Tamil: Ramachita	Kannada: Mullu Ram Phal Tamil: Paanghi Pazham Malayalan: Mullatha

2.1.1. *Annona squamosa*

Geographical distribution:

Annona squamosa L. (Figure 1) is inherent to tropical and subtropical areas and is distinct in tropical South America and West-Indies, Peru, India, Ecuador, Brazil, India, Mexico, the Bahamas, Bermuda, and Egypt. Further botanical data are presented in Table 2.

Morphology:

This is a semi-deciduous tree, an adult tree growing up to up 3–8 meters tall. Leaves are oblong-lanceolate 6–17 cm long and 3–5 cm in width and placed alternately often around diminutive petioles. The trees have a thin gray bark with greenish, juicy, drooping fruits, which are typically seen on a leafy stem than on the developed wood. Fruit can be round, heart-shaped, ovate, or conical, with a diameter of 5–10 cm, with many spherical protuberances. Fruits consist of blackish or dark brown seeds that are 1.3–1.6 cm long, which are smooth and lustrous [11, 12].

Figure 1. *Annona squamosa*- (A) plant, (B) flower, (C) fruit, (D) seeds

2.1.2. *Annona reticulata*

Geographical distribution:

Annona reticulata (Figure 2) is commonly found in tropical and subtropical climates. It is native to West Indies, India, South America, West-Indies, South Florida, Bahamas, Bangladesh, and Pakistan. In India, it is abundantly prevalent in West Bengal, Burma including other southern regions [10, 13]. Further botanical details are enumerated in Table 2.

Morphology:

It is a deciduous tree cultivated and known as a fruit-bearing tree. It grows up to 6.0 to 7.5 meters. It is a tiny tree with numerous lateral and glabrous branches. They have cylindrical trunks containing lenticels coated with very short coffee-colored hairs. They have sharp leaves which are oblong, lanceolate, membranous, and round or oval at the base. The lower surface of the leaves includes few spreading hairs whilst the upper surface is glabrous. Flowers may occur on the lateral side of the pedicel. They yield fruits resembling heart shapes, and unripe fruits have a characteristic yellow tint which after maturing transforms into yellowish red. Fruits are sweet, astringent, and edible. Fruits contain 40-60 seeds which are silky and blackish [14].

Figure 2. *Annona reticulata*- (A) plant, (B) flower, (C) fruit, (D) seed

2.1.3. *Annona muricata*

Geographical distribution:

Annona muricata (Figure 3) is the native species of the warmest tropical parts of North and South America. They are widely dispersed throughout the subtropical and tropical parts of the world, which includes India, Malaysia, and Nigeria. Further botanical information is enumerated in Table 2 [15].

Morphology:

Annona muricata is the most frequently grown species in the *Annona* genus. It is a short, thin, upright, evergreen tree that grows up to 5-10 meters tall with low branches and a round-open canopy. The brown stem is round and rough, with no short hair. They have glossy, large, and black oblong-ovate to cylindrical leaves with a short petiole. The blooms of this species are bigger than the flowers of the other two species listed above. The fruits of this species are greater than those of other species in the genus; they are conical, ovate, and compared to the other species listed above, the fruit tastes somewhat acidic and less sweet. The fruit is heart-shaped and is dark green while unripe and light green when mature features 127-170 dark-brownish seeds [16-18].

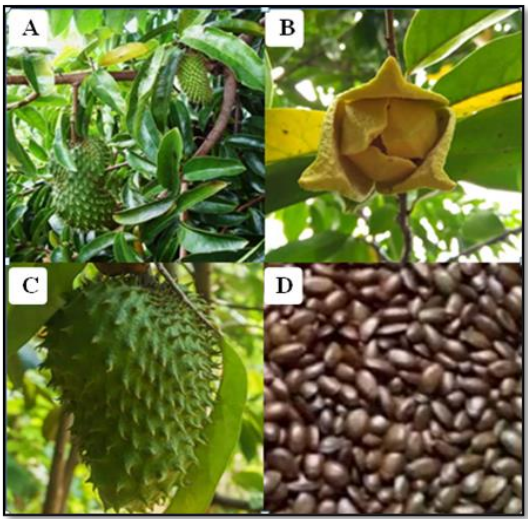

Figure 3. *Annona muricata*- (A) plant, (B) flower, (C) fruit, (D) seeds

2.2. Phytoconstituents Present in seeds of *Annona* Species

In recent decades, studies have revealed the existence of anticancer potency in *Annona* species due to the presence of Acetogenins; these acetogenins are particularly found in the seeds of *A. squamosa*, *A. reticulata*, and *A. muricata*; it is also known that various parts of these plants, including leaves, fruits, bark, roots, and bark, have medicinal values. These plants exhibit a dense or tiny concentration of primary and secondary metabolites such as lectins, cyclopeptides, alkaloids, phenolic compounds, and acetogenins (ACGs). Table 3 emphasizes the specific class of chemicals included in each species.

2.3. Reported Pharmacological Activities from Seeds of *Annona* Species

Earlier investigations have demonstrated that phytoconstituents of these plants have remarkable pharmacological properties including anticancer activity, immunosuppressive, pesticide, antiprotozoal, antibacterial, antimalarial, and anthelmintics, antiviral activity, and others. In recent years some of the extracted acetogenin compounds from the seeds of this species have been developed commercially as a treatment for oral herpes and treatment of infestations of head lice, fleas, and ticks. The seeds of these species are known to include acetogenins, lectins, cyclooligopeptides and cyclopeptides, alkaloids, phenols, etc. Several phytoconstituents have been found and isolated (Table 4).

Table 3. Phytochemical composition of A. squamosa, A. reticulata, and A. muricata seeds

***Annona* species**	**Bioactive compound**
	Phenolic acids and fatty acids
A. squamosa	Benzoic acid, Cis-vaccenic acid, Ellagic acid, Ferulic acid, Salicylic acid, Gallic acid, Heneicosanoic acid, Linoleic acid, Hepatadecene-(8)-carbonic acid, Hexadenoic acid, Palmitic acid, O-coumaric acid, Octadecenoic acid, Oleic acid, Stearic acid, Syringic acid, *ρ*-Hydroxybenzoic acid and (Z)-2,3-dihydroxy propyl ester [28, 35].
A. reticulata	Arachidic acid, behenic acid, oleic acid, heptadecanoic acid, linoleic acid, linolenic acid, myristic acid, palmitic acid, stearic acid and lignoceric acid [36, 37].
A. muricata	Cinnamic acid, caffeic acid, gallic acid, chlorogenic acid, coumaric acid, neochlorogenic acid, n-fatty acyl tryptamines, protocatechuic acid, and syringic acid [38, 39].
	Cyclopeptides
A. squamosa	Annosquamosin-A, Squamin A-B, Cyclosquamosins A-I, Squamtin A, Fanlizhicyclopeptides A-B, Met-cherimolacyclopeptide B [40-42].
A. reticulata	Cycloreticulin A-C, Glabrin-A [10, 43].
A. muricata	Annomuricatin A-L [44-46].
	Alkaloids
A. squamosa	*Annona*ine, Liriodenine, Corypalmine, Reticuline, Nornuciferine, Samoquasine a (-)-nonaine 8, Asimilobine, (-)-Nornuciferine or (-)-n-Methylasimilobine, (+)-Reticuline. Dopamine, Salsolinol [40, 47].
	Acetogenins
A. squamosa	Annosquacins A–D, Annosquatin A-B, Squamocin I-V, Squamoxinone-D, Squamoxinone-E, Quamocin P, Dieporeticenin B, Squamocins B To N, Coumarinoligans, Squamocin, Cholesteryl, Annotemoyin-1, Annotemoyin-2, Glucopyranoside, *Annona*cin, *Annona*cin A, *Annona*statin, Squamostatin D, Squamocin, Squamocin-$O_{1,}$ (2,4-Cis-Trans)-Bullatacinone, Squamostatin C, AnnoninI, Annonin VI, Squamostene-A, Reticulacin-1, Squamocin-$O_{2,}$Squamosinin-A, Annotemoyin-1, Annotemoyin-2, Annoglaxin, Epoxyrolin B, Murisolin, Neodesacetyluvaricin, Neo-Epoxyrolin, Annosquacin A-D, Annosquamin A-C, Annosquatin I-Iii, Annosquatin B, Annotemoyin-1, 2, Squamocin, Bullatacin/Squamocin, N-nonareticin, Cherimolin 1-2, Corepoxylone, Diepomuricanin A-B, Dieporeticenin, Dieposabadelin, Dotistenin, Glabrencin B, Squamocin-O1,Lepirenin, Bullatencin, Squamin A-B, Reticulatain 1-2, Squamocenin, Motrilin, Solamin, Squadiolin A-C, Cisannotemoyin 1, Squafosacin B-C, Squafosacin F-G, Squamocin B-K, Squamocin M, Squamoxinone-D, Squamocin-O2, Squamostanin A-D, Squamotin A-D, Uvarigrandin A, Squamostolide, Tripoxyrollin, Uvariamicin I-III, 12,15-Cis-Squamostatin A, Cherimolacyclopeptide B, Cyclosquamosin A, Annosquatin-IV-V, Muricin O, Squamosten B and Cyclosquamosin C-I [31, 48-57].

Table 3 continued

A. reticulata	Annomonicin, Trans-isomurisolenin, Rolliniastatin-1, 2, Annoreticuin, Squamocin, Squamosine, Rolliniastatin, Squamone, Bullatacin, Cis-/trans-isomurisolenin, Cis-/transmurisalinone, Cis-/trans-bullatacinone, Annoreticuin-9-one, Iso*Annona*reticin, 2, 4-cis-iso*Annona*reticin, 2, 4-trans-iso*Annona*reticin,Reticulacinone, Annomonicin,2, 4-cis-iso*Annona*reticin, Squamocin, Cis-/trans-isomurisolenin, Annoreticuin, Bullatacin,Cis-/transmurisalinone, Annomonicin, 2 squamone, Iso*Annona*reticin, *Annona*reticin, 2,-4-cis-iso*Annona*reticin, 2, 4-trans-iso*Annona*reticin, Solamin, Murisolin. Reticulacinone, Sitosterol, Daucosterol, dieporeticanin-1and 2, dieporeticenin, trieporeticanin [32, 51, 58-61].
A. muricata	Ronbusticin, Annomuricatin A, Cohibin A-D, Donhexocin, Muricatenol, Epomuricenins A-B, Corepoxylone, Epoxyrollin B, Annoglaxin, *Annona*cin, *Annona*cin-10-one, Iso*Annona*cin, Iso*Annona*cin-10-one, Goniothalamicin, Gigantetrocin, Gigantetrocin A-B, Cis-goniothalamicin, Arianacin, Javoricin, Murihexol, Muricatenol, 2,4-cis-gigantetrocinone, 2,4-trans-gigantetrocinone, 2,4-trans-iso*Annona*cin-10-one, Annomontacin, Longifolicin, Cis-annomontacin, *Annona*cinone, Xylomaticin. Epomuricenin A, Annocatacin A, Cis-*Annona*cin, Epomuricenin B, Annoreticuin-9-one, Arianacin, Corossolona, Gigantetrocin A-B, Muricatetrocin A-B, Muricatin A-D, Muricin A-I, Solamin, Bullatacilin, Bullatacin, Gigantecin, Annocatacin, (2,4-trans)-iso*Annona*cin, Murisolin, Muricatacin, Corossoline, Gigantetronenin, Corossolone, Longifolicin, Goniothalamicin, Muricatetrocin, Murihexol, *Annona*cin A, *Annona*cin, Decane, Undecane, Tridecane, (E)-2-Decenal (E,E)-2,4-Decadienal, Tetradecane, Pentadecane, β-Bisabolene, β-Sesquiphellandrene, (E)-Nerolidol, 1-Heptadecene, n-Octadecane, Heptadecaneetradecanoic acid, Nonadecane, 2-Nonadecanon, Hexadecenoic acid, methyl ester, Pentadecanoic acid, 1-Nonadecene, Hexadecanal, Heptadecanoic acid, 9,12-Octadecadienoic acid, 6-Octadecenoic acid, Octadecadienoic acid, 9-Octadecenoic acid, (Z)-9-Octadecenoic acid, ethyl ester, Hexadecanamide, Hexadecanoic acid, butyl ester, 1-Nonadecene, Octadecanal, Heneicosane, 6,9-Octadecadienoic acid, (Z)-9-Octadecenamide, Octadecanamide, 1-Eicosanol,Di-(9-octadecenoyl)-glycerol, Phthalic acid mono-2-ethylhexyl ester, Oxirane, hexadecyl, Humulane-1, 6-dien-3-ol, Glyceryl trioleate, (3-β)-Stigmast-5-en-3-ol, Bis (2-ethylhexyl) phthalate, Urs-12-ene, 9,19-cyclolanostan-3-ol, 24- methlene, Tirucallol, 9,19-cyclolanost-24-en-3-ol, Lupeol, and *β*-Amyrin [39, 62-72].

Table 4. Pharmacological activities of seed of *A. squamosa, A. reticulata* and *A. muricata*

Species	Activity	Screening method/model	Description	Phyto-constituent
Annona squamosa	Antioxidant Activity	DPPH free radical scavenging activity, ABTS Cation Decolorization Capacity, Hydroxyl radical scavenging assay, Total Phenolic and total Flavonoid content assay and Ferric ion reducing assay [73, 74].	Aqueous extract of seeds showed maximum Antioxidant activity by DPPH assay. Maximum total Phenolic content was exhibited by Chloroform-methanol extracts. Total flavonoid content was exhibited high in ethanolic extracts. Methanolic extract showed maximum antioxidant activity by ABTS Cation Decolorization Capacity and Hydroxyl radical scavenging assay. The seed oil through these three parameters indicated good antioxidant potential.	-
	Nutraceutical potential	Proximate and Nutritional Composition Analysis [75].	The seeds of *Annona squamosa* were evaluated for their nutritional contents and were found to have (19.60 mg/100g equivalent Ascorbic acid and so can be used as a good source of nutrition for daily intake.	-
	Hepatoprotective	Alcohol-induced liver injury in Sprague Dawley rat [76].	The study reported that Ethanol extract from seeds of *A. squamosa* have showed potential hepato-protective effect against alcohol-induced liver injury which may be attributed to its hepatoprotective and antioxidant activities.	-
		CCl_4 induced liver damage in rats [77].	The study revealed that treatment of CCl_4 induced liver damage in rats with hydro-alcoholic seed extract of *A. squamosa* indicated the recovery of hepatic cells against hepatic damage.	-
	Pesticidal activity	Spraying [78].	The results showed that on spraying aqueous extract of *Annona squamosa* at 90% concentration on leaf mealworms and cricket it was observed that the extract showed good insecticidal potential, and the study concluded that it can be used as a cost effective and environment friendly bio pesticide.	-
	Nematicidal activities	Nematicidal Bioassays against PWN, Nematicidal Bioassays against RKN [53].	Eight new compounds were isolated from the Methanolic seeds extract of *A. squamosa* and they showed strong Nematicidal activities against Pine wood nematode (PWN) and Nematicidal activities against RKN (root-knot nematode).	Squamocin J-M Squamostatin-A Squamocin G Squamocin H Squamosin
	Antifungal activity	*In vitro* assay [53].	The isolated compounds from the methanolic seed extract of *A. squamosa* inhibited the development of sporangium and zoospore of *Phytophthora infestans* in a dose dependent manner.	Squamocin G Squamocin H Squamosin
	Pediculicidal activity	*In-vitro* method using head lice [79].	The isolated compound from the hexane extract of the seeds, the isolated compound oleic acid was able to kill the head lice at 49 minutes, the one oleate ester of triglyceride was able to kill the lice at 11 minutes and the crude extract was able to kill the head lice at 30 minutes intervals.	Oleic Acid Oleate Ester
	Anti-feedant activity	Leaf disc choice bioassay, Leaf dip bioassay, Drench bioassay [80].	Ethanolic extract from seeds of *A. squamosa* showed remarkable antifeedant activity against *Chrysoperla carnea* and *Orius insidiosus* through direct spray and residual contact test and results indicated that *Orius insidiosus* larvae were sensitive to the *extract* than the *Chrysoperla carnea.*	-

Table 4 continued

Antibacterial	Disc diffusion method [81].	Petroleum extract of the *Annona squamosa* seeds were able to show zone of inhibition of 24mm against *P. aeruginosa*, 30mm against *S. β-haemolytica* and 23 mm against *Klebsiella spp.* at 200 µg/disc.	Annotemoyin-1, Annotemoyin-2, quamocin, Cholesteryl Glucopyranoside
	Agar disc diffusion method [82].	n- Hexane extract of *Annona* seeds showed broad spectrum activity among these *Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia, Bacillus cereus* and *B. anthracis* were more susceptible.	-
Anthelmintic activity	Invitro test for Anthelmintic bioassay by Egg hatch test [83].	An isolated compound from the methanolic extract of *A. squamosa* seeds inhibited egg hatching of *Haemonchus contortus and* was also proved to have potential anthelmintic activity at 25 mg mL^{-1}.	-
Anti- hypertensive activity	nor epinephrine (NE) - induced contractions of rat aorta with/without endothelium [40].	Cyclosquamosins-B, an isolate from the n- butanol fraction of methanolic extract of seeds showed vasorelaxation activity in the mentioned model.	Cyclosquamosins B
Anti-cancer activity	MTT assay [54].	Isolated acetogenins from seeds of *Annona squamosa* exhibited potent cytotoxicity against the growth of A549/Taxol cells compared to Verapamil which have clinical applications.	Annosquamin A-B, Annosquacin B, Annosquacin D quamostanin A-B Squamostatin-E
	MTT assay [84].	Chloroform and petroleum Ethanol fractions from the methanolic extracts showed potential *In vitro cytotoxicity* against Human lung carcinoma, Cervix carcinoma, Breast carcinoma, Hepatoma carcinoma and Gastric adenocarcinoma cell lines.	Annosquatin-I Annosquatin-II Uvarigrandin A Bullatacin Squamostatin-A Squamostatin-D
	MTT Assay [85].	Showed Cytotoxic activity on A549 lung cancer cell lines.	Squamocin-I- III Squamoxinone-D
	MTT assay [31].	The isolated compounds showed potent Cytotoxic activity on H460 human cell lines.	Squamocin-IV Squamocin-V Moxinone-E
	In vivo - H22 Xenograft model [48].	The isolated compound demonstrated significant antitumor activity in the H22 Xenograft model.	Annosquamin B Annosquatin B Bullatacin

Table 4 continued

	In vivo - H22 hepatoma cells transplantation tumor model [86].	The total acetogenins isolated from the seed extract showed inhibitory effect on the H_{22} bearing mice.	-
	MTT assay [87].	Exhibited significant Cytotoxic activity against various cancer celllines among them Annosquacin-I with IC_{50} $1.2X10^{-2}$ μg/ml showed maximum inhibition against Human lung carcinoma (A-549) similarly Annosquatin-I, Annosquatin-II Uvarigrandin-A and Bullatacin showed cytotoxicity against SMMC-7721- human hepatoma carcinoma with IC_{50} of $1.1X10^{-1}$, 3.9×10^{-1}, 2.9×10^{-3} and 4.8×10^{-3} respectively, also Squamostatin-A showed significant cytotoxicity against Human breast carcinoma (MCF-7) with IC_{50} of 1.5×10^{-1}, Bullatacin, squamostatin-D also indiacated cytotoxicity against Human lung carcinoma (A-549) with IC50 value of 4.6×10^{-2}.	Annosquacin-I Annosquatin-I Annosquatin-II Uvarigrandin-A Bullatacin Squamostatin-A Squamostatin-D
	MTT method [30].	The isolated compounds showed potent Cytotoxic activity against Human Gastric Cancer Cell (BGC-803), Protein profile of human hepatocarcinoma cell lines (SMMC7721), hepatocellular carcinoma (BEL-7402).	Squamocin-IV Squamocin-V Squamoxinone-E
	MTT assay [48].	Four isolated compounds from the *Annona* seeds were evaluated for anti-tumor activity against various cancer cell lines and Squamocin-I showed IC_{50} value of 1.23 μg/ml against human liver carcinoma(BEL-7402), Squamocin-II indicated potent antitumor activity against human liver carcinoma (SMMC7721) with IC_{50} of 1.08 μg/ml, Squamocin-III showed significant anticancer potential with IC_{50} value of $4.9X10^{-2}$ μg/ml against human lung cancer (H460) and Squamoxinone-D showed antitumor activity against human liver carcinoma (HepG2) with IC_{50} 0.74.	Squamocin-I Squamocin-II Squamocin-III Squamoxinone-D
	MTT assay [88].	The assay for cytotoxicity against human colon cancer (HCT) revealed that Squamostatin A has IC_{50} of $3.97 X 10^{-3}$, Squamostatin B showed promising cytotoxicity against human prostate adenocarcinoma (PC-3) $7.33 X10^{-4}$.	Squamostanin A Squamostanin B
	MTT assay [89].	Isolated compounds from the seed extract have shown selective cytotoxicity against multiple drug resistance cancer cell lines like liver cancer hepatocellular carcinoma and multiple drug resistance breast cancer cell lines with IC_{50} values at 1.79 µM 4.04 µM.	Annosquatin III Squamocin P
	MTT assay [87].	All the nine compounds were screened for cytotoxicity against three multi drug resistance cancer cell lines lung cancer, liver cancer and breast cancer among these squamotin A, squamotin D, gigantecin, and muricin O shown more cytotoxicity against liver cancer SMMC 7721/Adr with IC_{50} of 2.56, 1.43, 15.45 and 5.43µmolL^{-1} respectively. squamotin B, annosquatin V, annosquatin IV and squamosten B showed cytotoxicity against breast cancer MCF-7/Adr with IC_{50} values 5.23, 2.07, 4.71 and 4.03 µmolL^{-1} respectively. Squamotin C showed cytotoxic activity against lung cancer A549/T cell lines with IC_{50} value of 11.04 µmolL^{-1}.	Squamotin A Squamotin B Squamotin C Squamotin D Annosquatin IV Annosquatin V Muricin O Squamosten B Gigantecin

Table 4 continued

		MTT assay [90].	Three isolated compounds from seeds of *Annona squamosa* seeds extract were evaluated for their invitro anticancer activity SMMC, A54 and MCF and results indicated that compounds showed maximum efficacy at Inhibition concentrations of 0.163 μM, 0.064 μM and 0.057 μM respectively.	Annotemoyin L annotemoyin Y annotemoyin X
	Anti-inflammatory activity	MTT assay [91].	The known isolated compound from seeds of *Annona squamosa* indicated good Inhibitory action on production of pro-inflammatory cytokines within lipo-polysaccharide and Pam3Cys-stimulated J774A.1 macrophages.	Cyclosquamosin D
	Biosorbent activity	X-ray diffraction (XRD) technique [92].	The biosorbent activity of *A. squamosa* seed powder was evaluated against aqueous solution containing cadmium, the test revealed that the powder was effective in removing cadmium from the aqueous solution and was characterized using XRD and optimum dosage, contact time and concentration of cadmium was evaluated using adsorption isotherm model. The study revealed that the seed powder was cost efficient and eco-friendly.	-
Annona reticulata	Antidiabetic activity	Streptozotocin induced diabetes in rats [93].	The treatment of diabetes induced rats with 50 and 100mg of ethanolic *Annona reticulata* seed extract caused anti-oxidative, antinflammatory, anti-hyperlipidemic and anti-diabetic effect.	-
	Biosorbent activity	Sulphuric acid–modified *Annona reticulata* seed as a biosorbent [94].	The sulphuric acid modified *Annona reticulata* seed (SMARS) at a dose of 1.0 g/L, at temperature 30^0 C and 6.0 pH were recorded as optimal conditions for the removal of Zn (II) ion in 50 mg/L concentration and the absorption capacity of SMARS was able to remove 223.1 mg g^{-1} and can be used as an effective agent for the removal of effluents.	-
		Adsorption of Auromine-O Dye [95].	The biomass of 450 μ size prepared using *A. reticulata* seed were able to adsorb 85-86% of the Auromine-O Dye. The biosorbent activity of the biomass increased with increase in the dose of the sorbent used for removal of the dye. The study reveals that the seed powder can be used for effective removal of Auromine-O Dye from aqueous solutions.	-
	Antiepileptic Activity	Pentylene tetrazole induced convulsion model [96].	The methanolic seed extracts of 200 mg/kg and 400mg/kg were found to have delayed the onset of tumor and duration of tumor. The higher dose of extract was found inhibited the Pentylenetetrazol induced convulsion.	-
	Anti-angiogenic activity	*In-vivo* anti-tumor model [97].	N-hexane extract of the seeds at 20mg/kg I.P showed good anti-angiogenic activity through *In-vivo* model by histopathological tests and tumor mass measurements.	-
	Wound healing and anti-marking activity	Creating wounds in par vertebral area [98].	Ethanolic extract of *Annona reticulata* seeds in combination with honey, ghee and neem oil showed potential anti-marking and wound healing activity.	-
	Insecticidal activity	Bioassay using *Zabrotessubfasciatus* [98].	The ethanolic extract of *Annona reticulata* seed presented 71% mortality with LC_{50} and LC_{90} of 776.80 mg kg^{-1} and 994.64 mg kg^{-1} respectively.	-
	Anthelmintic activity	In-vitro activity against *Pheretimaposthuma* [99].	The ethanolic and chloroform seeds extracts of *Annona reticulata* were evaluated for their Anthelmintic activity against *Pheretimaposthuma.* The results of the study indicated that ethanolic extract (12.5 mg/ml) showed potent activity by inducing paralysis and mortality.	-
	Insect repellent activity	Toxicity test against *Callosobruchus maculatus* [100].	The ethanolic seed extract of *A. reticulata* showed potent contact toxicity and fumigant toxicity with mean repellency of 84%.	-

Table 4 continued

Annona muricata	Antioxidant activity	Trolox equivalent antioxidant capacity (TEAC), DPPH free radical scavenging activity and Ferric reducing antioxidant activity (FRAP) [101].	The methanolic seed extracts of the *Annona muricata* seeds showed good free radical scavenging activity compared to hexane, ethanolic and ethyl acetate extracts, moreover the methanolic extract showed good TEAC (0.905±0.029 mmol Trolox/g) and FRAP (1100.6 ± 9.3 µ Mol Fe2+/g) activities.	-
		Total Phenolic content, Total Flavonoid content and total antioxidant activity by ABTS and DPPH free radical scavenging activity [102].	The study revealed that the ethanolic extract of *Annona muricata* seeds showed Total phenolic content of 282.71 ± 8.64 mgGAE/g and total flavonoid content of 86.57 ± 3.20 mg QE/g. It also showed good total antioxidant activity by DPPH and ABTS (341.57 ± 6.90 AAE/100g DW and 382.20 ± 9.71 mg AAE/100g DW.	-
	Anti-bacterial activity and anti-fungal activity	Kirby- Bauer disc diffusion method [103].	Antibacterial assay of terpenoids extracted from the seeds of *A. muricata* against the known strains of bacteria's such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*. The results showed that *Pseudomonas aeruginosa* and *Escherichia coli* were very sensitive to the extracts.	Terpenoids
	Larvicidal activity	Larvicidal assay [24].	Ethanolic extract from *A. squamosa* seeds extract showed potent larvicidal activity against *Aedes albopictu* and *Aedes aegypti* with lethal concentration-50 of 3.41 µg mL^{-1} and 26.75 µg mL^{-1} respectively.	-
		Mosquito larvicidal and toxicity bioassay [104].	The study concluded that the *Annona muricata* saline aqueous (0.9%) extract showed potent Larvicidal activity on *Aedes aegypti* with LC_{50} concentration of 0.009 mg/mL It was also concluded that the insecticidal activity is because of presence of lectin molecules.	Lectin
	Anticancer activity	Testosterone propionate (Tp)-induced benign prostatic hyperplasia [62].	The study reported that, on treating adult male wistar rats with Tp-induced benign prostatic hyperplasia with hexane fractions of *Annona muricata* seeds there was significant reduction in antioxidant indices inflammatory and prostatic weight, and it also concluded that it may also serve as a novel agent in treatment of benign prostatic hyperplasia.	-
	Cytotoxicity	*In vitro* assay [105].	The methanolic extract of *A. muricata* seeds were evaluated for their activity against MCF-7 and MDA-MB-231 using Invitro assays. The reports suggested that, at 320µg/mL the extract showed 80% of inhibition, furthermore the extract also showed G0/G1 cell cycle arrest and increased apoptosis.	-
		In vitro assay [106].	The study concluded that ethanolic and chloroform extract of *Annona muricata* seeds have potent anticancer activity against SKG cell lines with maximum inhibit concentration of 3.8µg/mL and 2.6µg/mL respectively.	-
		In vitro assay [106].	The study reported that the chloroform fraction from methanolic extracts of *Annona muricata* seeds has Cytotoxic activity against MDA-MD-231, 4TI and BT-549 with IC_{50} of 2.5±0.14, 4.8±0.3 and 4.5±0.16µg/mL.	-

3. Novel Drug Delivery Systems of *Annona* Species

3.1. *Annona squamosa*

Copper nanoparticles of *A. squamosa* aqueous extract has been reported to be an efficient antibacterial agent against the plant-derived bacterium *Xanthomonas oryzae* [19]. Green-generated manganese oxide nanoparticles from *A. squamosa* seeds has been shown to inhibited *Pactobacterium carotovorum* more effectively than streptomycin and tetracycline [20]. Microencapsulation of *A. squamosa*, hexane, and ethanol seed extracts were shown to be poisonous to *Tetranychus urticae*, and the research findings showed that the microencapsulation had comparable activity as the hexane extract and may be utilized as an environmentally friendly and effective bio pesticide [21]. Palladium nanoparticles synthesized by chemical and green synthesis methods from *A. squamosa* seeds were tested for cytotoxicity against a Zebrafish model, and the results showed that the oxidative damage caused by the green synthesized nanoparticles was significant when compared to the chemical synthesized nanoparticles [22]. The antibacterial activity of metal silver nanoparticles prepared from the aqueous extract of *Annona squamosa* seeds was studied, and the results showed that the nanoparticles have significant antibacterial activity against clinical pathogens such as *Bacillus subtillis*, *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus*, and *Vibrio cholera*. Silver nanoparticles were also shown to have a synergistic impact when used with commercial antibiotics [23]. Silver nanoparticles derived from aqueous seed extract of *A. squamosa* showed antibacterial and larvicidal actions against *K. pneumonia*, *S. aureus*, and *Anopheles stephensi* III and IV instars, respectively [24]. The impact of silver nanoparticles derived from *Annona squamosa* aqueous seed extract on seed germination, root elongation, and the production of photosynthetic pigments in *Phaseolus vulgaris* revealed that pretreatment of seed with silver nanoparticles at 60 mg L^{-1} was most beneficial [25].

3.2. *Annona muricata*

Silver nanoparticles derived from the aqueous extract of the *Annona muricata* seed have been shown to exhibit antibacterial action against both gram-positive and gram-negative bacteria, as well as substantial antifungal activity [26].The green-produced manganese oxide nanoparticles from *Annona muricata* seed demonstrated high antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. The research also revealed that the nanoparticles outperformed the common medication chloramphenicol. The green synthesized manganese oxide nanoparticles from *Annona muricata* seed showed better activity against *Staphylococcus aureus* than the chloramphenicol and showed similar inhibitory activity as that of the standard against *Escherichia coli* [27].

4. Conclusions

Annona species plants like *A. squamosa*, *A. reticulata*, and *A. muricata* have been widely explored for their medicinal and pharmacological effects. The biological activities of seeds were given specific emphasis in this short review since they comprise the bulk of primary and secondary metabolites. The seeds of these three plants have been shown to have anti-cancer, antioxidant, anti-diabetic, pesticide, and anthelmintic properties. Because information regarding seed activities was limited and dispersed, it was required to consolidate for researchers working in drug discovery and medical product development to leverage the biological activities of these plants. The current analysis showed considerable research activities conducted on *Annona* species seeds, as well as their traditional and therapeutical implications. Furthermore, the current literature review demonstrated that *Annona* species seeds remain underused and need to be further explored for their positive potential therapeutic actions.

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Conflict of Interest

The authors declare no conflicts of interest regarding this literature survey.

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