Journal of Advanced Pharmaceutical Sciences
Journal homepage: https://japs.journals.ekb.eg/

Review article

Annona squamosa L.: A promising herbal remedy – insights into its biological activities and phytochemical composition

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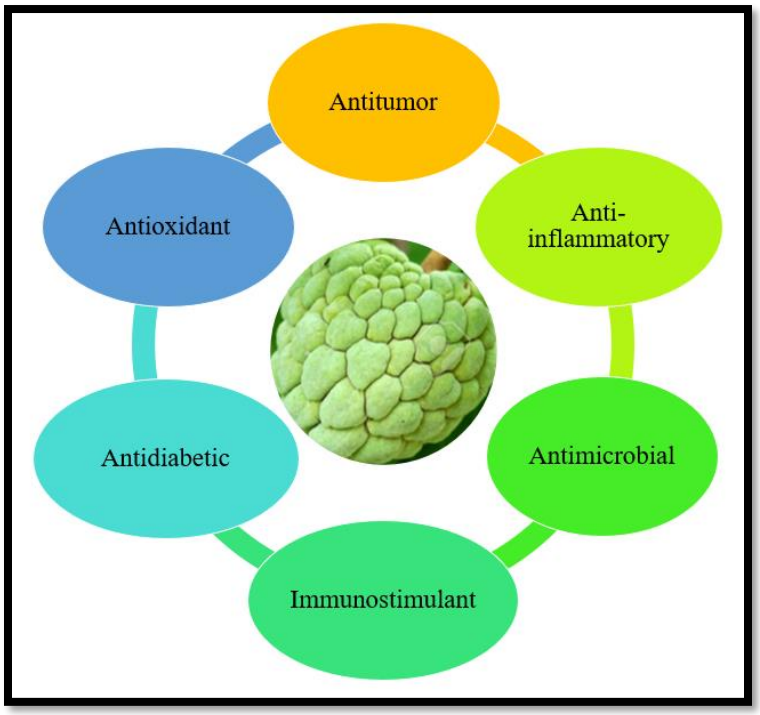
Abstract



Annonaceae is a large, prominent family within the Magnoliales order, containing many genera. Among these, the genus *Annona* holds significance for its substantial diversity and traditional medicinal value. *Annona squamosa* L. is one of the most common species of this genus. This tropical species, commonly known as the sugar apple, exhibits distinct morphological features. Phytochemical investigations of *A. squamosa* revealed the presence of acetogenins, alkaloids, diterpenes, and cyclopeptides in various plant parts. Acetogenins, found mainly in seeds and representing the major active constituents, possess distinctive structures and biological activities. Alkaloids, predominantly isolated from leaves, represent the second major class of *A. squamosa* active constituents. *A. squamosa* exhibits a wide array of pharmacological activities encompassing anti-tumor, anti-inflammatory, antioxidant, antidiabetic, antimicrobial, antiviral, immunomodulatory, and wound-healing properties. This comprehensive review highlights the botanical characteristics, phytochemical composition, and diverse pharmacological activities of *A. squamosa* and aims to be a guide for further research on *A. squamosa*.

Keywords: Annonaceae, Annona Squamosa, Annona, Acetogenins

Received 8 December 2023 Accepted 27 January 2024 Published 29 January 2024

DOI 10.21608/JAPS.2024.254019.1008
ISSN: 3009-7061

1. Introduction

Medicinal plants have been utilized since ancient times for different therapeutic purposes [1]. They still act as the primary healthcare method for about 85% of the world population due to their low cost [2]. Additionally, they serve as an important source for the development of modern medicine, with approximately 80% of the synthetic drugs derived from natural sources [3]. So, focusing on the traditional uses of plants and studying their active metabolites may provide a rational for their known uses and help to discover new therapeutic agents.

Annonaceae plants are one of the medicinal plants with an increasing utilization rate nowadays [4]. It is considered the largest family of the Magnoliales order [5], including over 2000 species and 120 genera [6]. It is subdivided into 4 subfamilies, Annonoideae, Malmeoideae, Anaxagoreoideae, and Ambavioideae, and 15 tribes [7].

Annona L. is a highly significant genus within the Annonaceae family, renowned for its edible fruits and medicinal properties [8]. This genus is indigenous to tropical regions and is characterized by its substantial diversity, encompassing around 166 species. Common species within this genus include *A. cherimola*, *A. muricata*, *A. reticulata*, *A. squamosa*, *A. glauca*, *A. montana*, *A. scleroderma*, *A. glabra*, and *A. purpurea* [9].

Sugar apple, the common name of *A. squamosa*, is recognized as one of the most extensively distributed species within *Annona* genus [10]. It is a small deciduous tree, about 3-6 m in height, with an open crown on which the branches are arranged irregularly. The leaves, which are about 5-15 cm long and 2-5 cm wide, are oblong or lanceolate with a blunt tip and arranged on short petioles. The flower is about 2.5-3.8 cm long with yellow-green petals on the outside and pale-yellow inside and purple spots at the base. The fruit, which is about 6-10 cm long, has a round or conical shape with a pale green or bluish-green pericarp and a creamy-white, juicy, and sweet pulp. In most cases, the fruit contains black or dark-brown seeds about 1.25 cm long [11].

A. squamosa is cultivated in tropical South America, southern Mexico, and occasionally in southern Florida. In the 17th century, it has been introduced into southern China, Queensland, Australia, Polynesia, Hawaii, tropical Africa, Egypt, and the lowlands of Palestine [11].

2. Taxonomy of *A. squamosa* [12]

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida (Dicotyledons)
Order: Magnolialesles
Family: Annonaceae (Custard-apple family)
Genus: *Annona* L.
Species: *A. squamosa*

3. *A. squamosa* as a traditional medicine

Traditionally, *A. squamosa* has been utilized to relieve numerous health conditions. The leaf decoction was reported to be used in cases of vomiting and other digestive system disorders. Furthermore, it has been used to reduce fatigue and muscle aches, as well as in the treatment of certain skin disorders such as abscesses. Moreover, the decoction was used to regulate fever and control convulsions. One of the most common traditional uses of *A. squamosa* is the utilization of its leaf decoction as an antimalarial agent, that has been widely used [4]. In different cultures, *A. squamosa* has been used for its analgesic, antihelmintic, anti-inflammatory, antimicrobial, antirheumatic, carminative, digestive, and headache-controlling properties. Furthermore, different parts of *A. squamosa* have been extensively reported to be used in the treatment of various types of cancer [13].

4. Phytochemical literature of *A. squamosa*

Phytochemical investigations have revealed that *A. squamosa* primarily contains acetogenins, diterpenes, alkaloids, essential

ISSN: 3009-7061

oils, and cyclopeptides as its major constituents [14]. Upon reviewing the phytochemical literature of *A. squamosa*, it has been observed that acetogenins and cyclopeptides are predominantly found in the seeds, while the leaves are a rich source of alkaloids, and diterpenes are commonly isolated from the bark and stem. Moreover, the majority of volatile oils were reported in fruit pulp and leaves. [14-16].

4.1. Acetogenins

The primary bioactive compounds of *Annona* are acetogenins [17]. Acetogenins have a structure derived from long-chain fatty acids and share common characteristics such as a long aliphatic chain with a butyrolactone ring. Additionally, they are substituted with one or more tetrahydrofuran rings, epoxide rings, hydroxyl groups, or double bonds [18]. Acetogenins are categorized into four groups based on the substitutions present along the hydrocarbon chain [19]. The first category of acetogenins is called linear acetogenins, where the aliphatic chain is substituted with oxygenated groups such as hydroxyls, ketones, epoxides, or a double bond. However, it does not include a furan ring [20]. The second category is mono tetrahydrofuran acetogenins, which have one tetrahydrofuran ring substitution. The third category, bis-tetrahydrofuran acetogenins, has two tetrahydrofuran rings, either adjacent or non-adjacent. Lastly, the fourth category is miscellaneous acetogenins, which encompasses acetogenins with tri-tetrahydrofuran rings or a combination of tetrahydrofuran and tetrahydropyran rings [20]. **Table 1** shows the recently isolated acetogenins.

Acetogenins exhibit a wide range of biological and pharmacological activities, including insecticidal, antimicrobial, fungicidal, anti-inflammatory, and cytotoxic activity [21-24]. Annotemoyin-1, annotemoyin-2, and squamocin, isolated from *A. squamosa* seed, were reported to be effective antibacterial agents that have activity against *Pseudomonus aeruginosa* and *Escherichia coli* [23]. Furthermore, squamocin A, squamocin G, and squamostatin A, isolated from *A. squamosa* seed, showed antifungal activity against *Bursaphelenchus xylophilus* and *Meloidogyne incognita* and can be effective against many plant diseases caused by fungal infections [21]. Despite the numerous activities of acetogenins, their cytotoxicity and antitumor activity remain the most important points that studies have focused on. It was reported that acetogenins inhibit NADH enzyme, which is over-expressed in cancer cells, inhibiting ATP production and causing cell death [25]. Additionally, squamoxinone-D was identified to have selective activity against the H460 cell line (lung cancer) [26]. Both squadiolins A and B were reported to exhibit a cytotoxic effect on MDA-MB-231 (breast cancer) cells [27]. Squamocin P and annosquatin III, extracted from the seed, have a selective cytotoxic effect on SMMS 7721/T (hepatocarcinoma) and MCF-7/ADR (breast cancer) cell lines, respectively [28]. Moreover, acetogenins were found to be effective against some multidrug-resistant cancer cell lines, such as annotemoyin X, that showed potent cytotoxic activity against SMMC 7721, A549, and MCF-7 cell lines.

Table 1: Some of the previously isolated acetogenins from *A. squamosa*

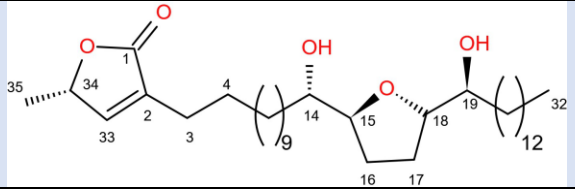
	Name	Structure	Plant part
1	Annotemoyin L		Seed [29]

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Table 1: Continue

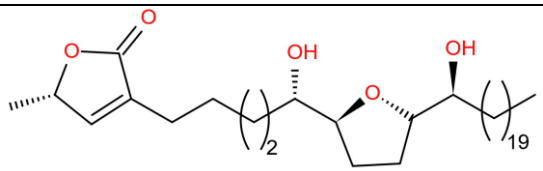
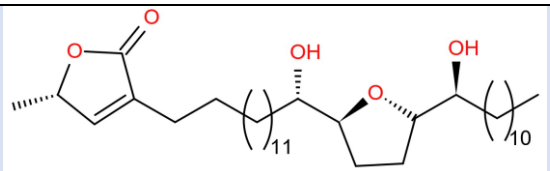
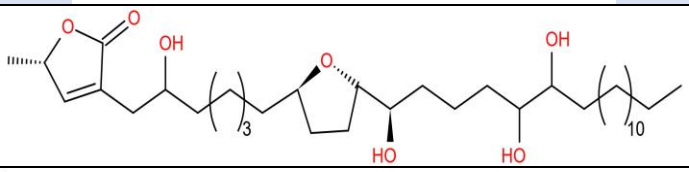
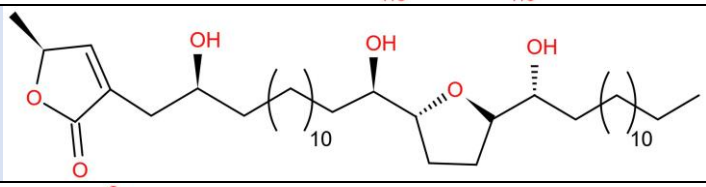
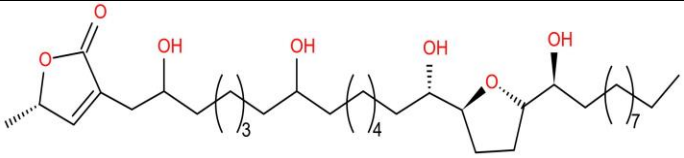
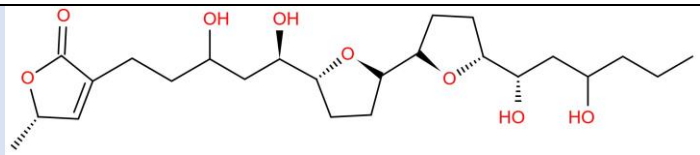
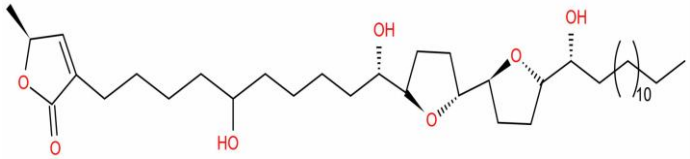
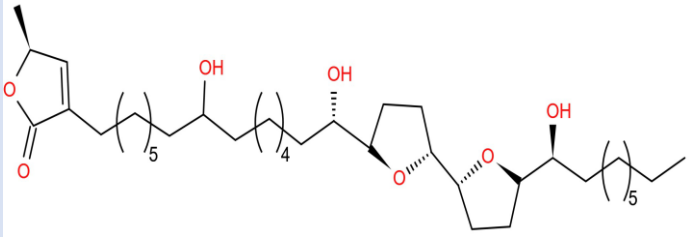
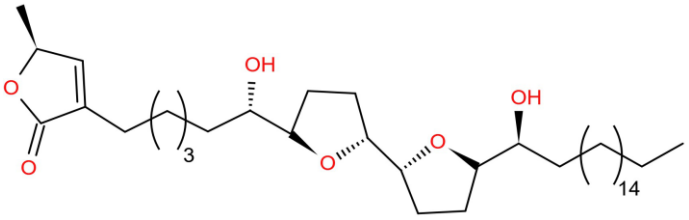
2	Annotemoyin Y		Seed [29]
3	Annotemoyin X		Seed [29]
4	Muricin O		Seed [30]
5	Squamocin-V		Seed [31]
6	Squamosten B		Seed [30]
7	Squamocin P		Seed [28]
8	Squamocin-IV		Seed [31]
9	Squamotin A		Seed [30]
10	Squamotin B		Seed [30]

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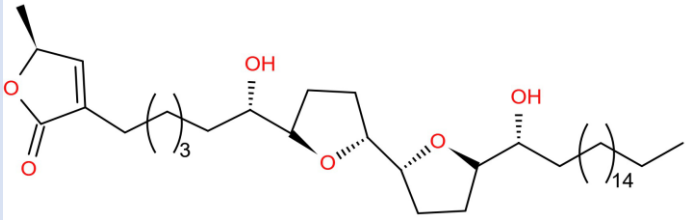
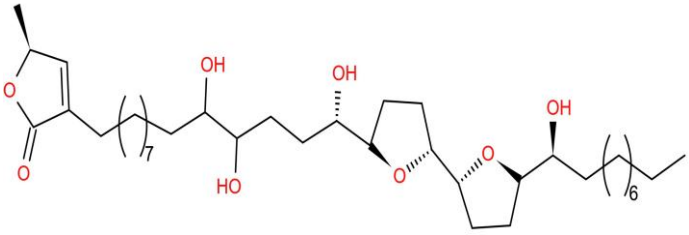
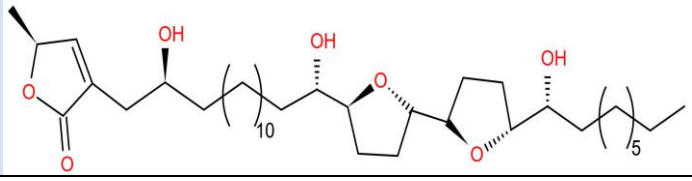
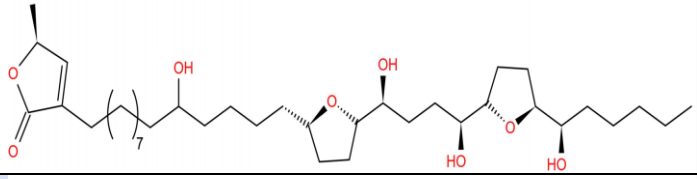
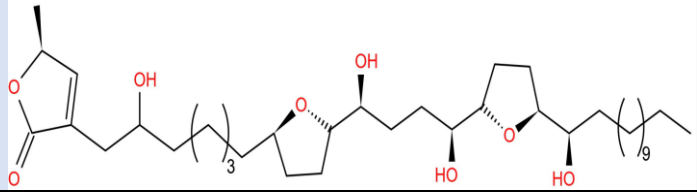
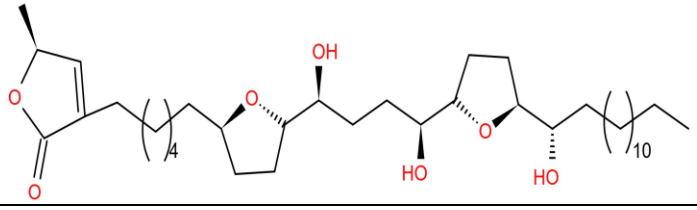
Table 1: Continue

11	Squamotin C		Seed [30]
12	Squamotin D		Seed [30]
13	Squamoxinone-E		Seed [31]
14	Annosquatin-III		Seed [28]
15	Annosquatin-IV		Seed [30]
16	Annosquatin-V		Seed [30]

4.2. Alkaloids

The second major active component found in *A. squamosa* is alkaloids [32]. Alkaloids have been predominantly extracted from the leaves of the plant, with aporphine alkaloids being the most prevalent type of alkaloids in *Annona* genus [33]. *A. squamosa* alkaloids have been studied for their various biological activities. They exhibit antibacterial, antioxidant, and cytotoxic activity [34, 35]. 6, 7-Dimethoxy-1-(α-hydroxy-4-methoxybenzyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline and coclaurine showed excellent cytotoxic activity against HepG-2, MCF-7, and HCT-116 cell lines. Additionally, *O*-methylarmepavine alkaloid was reported to be effective against *Leishmania chagasi* [36]. Moreover, *N*-nitrosoxylopine, roemerolidine, and duguevalline, which were isolated from *A. squamosa* leaves, are known for their antimalarial activity against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* [37]. It was also

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reported that some alkaloids, such as lanuginosine, (+)-*O*-methylarmepavine, and *N*-methyl-6, 7-dimethoxyisoquinolone from *A. squamosa* twigs, can modulate the immune system response through stimulation of macrophages and enhancement of the proliferation of B and T cells [38]. Furthermore, other alkaloids such as (+)-*O*-methylarmepavine, *N*-methylcorydaldine, and isocorydine from *A. squamosa* twigs have anti-ulcer activity as they decrease gastric acidity and the digestive enzymes level [39]. Their effects are comparable to omeprazole [39]. **Table 2** shows some of the previously isolated alkaloids from *A. squamosa*.

Table 2: Some of the previously isolated alkaloids from *A. squamosa*

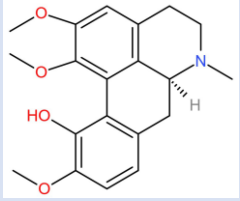
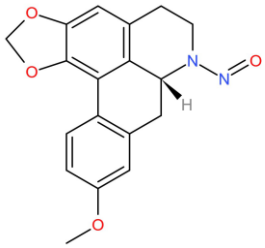
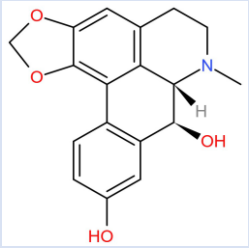
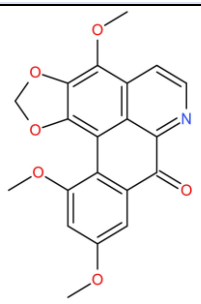
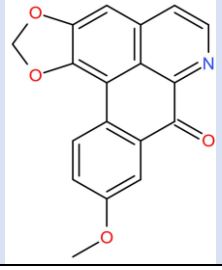
	Name	Structure	Plant part
1	Isocorydine		Stem, Leaves [40]
2	*N*-Nitrosoxylopine		Bark [41]
3	Roemerolidine		Bark [41]
4	Duguevalline		Bark [41]
5	Lanuginosine		Twigs [39]

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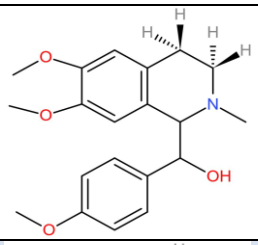
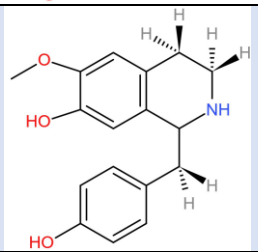
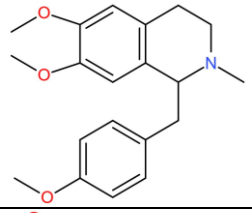
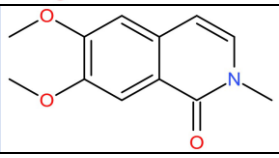
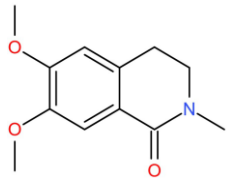
Table 2: Continue

6	6, 7-Dimethoxy-1-(α-hydroxy-4-methoxybenzyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline		Twigs [42]
7	Coclaurine		Leaves [43]
8	*O*-Methylarmepavine		Twigs [39]
9	*N*-Methyl-6,7-dimethoxyisoquinolone		Twigs [39]
10	*N*-Methylcorydaldine		Twigs [39]

4.3. Diterpenoids

A. Squamosa diterpenoids are concentrated in plant stems and bark with *ent*-kaurane diterpenoids being the most prevalent type [14]. Diterpenoids contribute to the different activities of *A. squamosa*. 17-Hydroxy-*ent*-kaur-15-en-19-al, 15,16-epoxy-17-hydroxy-*ent*-kauran-19-oic acid, *ent*-kaur-16-en-19-oic acid, and 16*α*,17-dihydroxy-*ent*-kauran-19-al were reported to be promising cytotoxic agents against human lung cancer (95-D) and ovarian cancer (A2780) cell lines [44]. 16*α*, 17-Dihydroxy-*ent*-kauran-19-oic acid, *ent*-kaur-16-en-19-oic acid, and *ent*-kauran-15-en-19-oic acid, from pericarp oil, were reported to exhibit a cytotoxic activity by induction of apoptosis and cell cycle arrest [45, 46]. Additionally, 16*β*, 17-dihydroxy-*ent*-kauran-19-oic acid was found to be effective against the replication of HIV in H9 lymphocyte cells [47]. It was also reported that *A. squamosa* diterpenoids, as *ent*-kaur-16-en-19-oic acid and 16*α*-hydro-19-al-*ent*-kauran-17-oic acid, may be of benefit for atherosclerosis patients as they inhibit platelet aggregation [48]. **Table 3** shows some of the previously isolated diterpenoids from *A. squamosa*.

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Table 3: Some of the previously isolated diterpenoids from *A. squamosa*

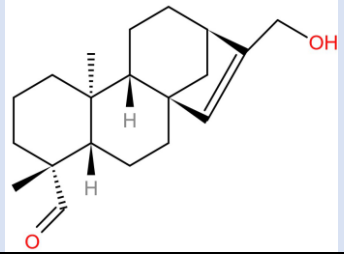
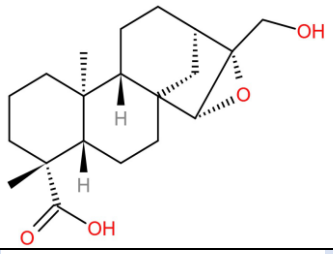
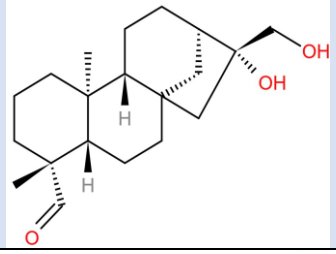
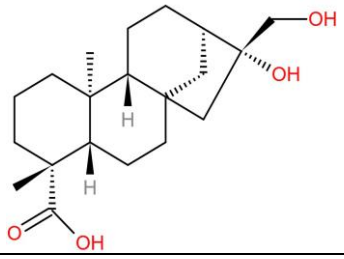
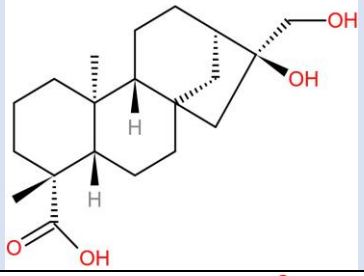
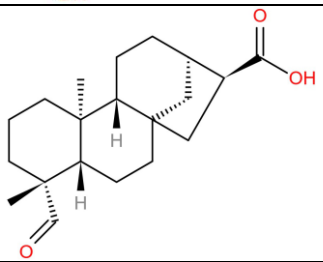
	Name	Structure	Plant part
1	17-Hydroxy-*ent*-kaur-15-en-19-al		Bark [44]
2	15,16-Epoxy-17-hydroxy-*ent*-kauran-19-oic acid		Bark [49]
3	16*α*,17-Dihydroxy-*ent*-kauran-19-al		Bark [44]
4	16*α*,17-Dihydroxy-*ent*-kauran-19-oic acid		Stem [50], pericarp [45]
5	16*β*,17-Dihydroxy-*ent*-kauran-19-oic acid		Stem [50]
6	16*α*-Hydro-19-al-*ent*-kauran-17-oic acid		Stem [50]

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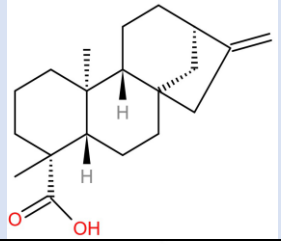
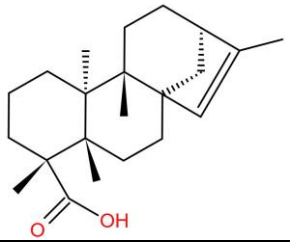
Table 3: Continue

7	*Ent*-kaur-16-en-19-oic acid		Stem [48]
8	*Ent*-kauran-15-en-19-oic acid		Pericarp [46]

4.4.Cyclic peptides

Cyclic peptides are peptides with ring structures that are formed by linking the peptides ends together either by amide bond, lactone, ether, thioether, or disulfide bonds [51]. They are considered among the most important *A. squamosa* active metabolites with many pharmacological activities. Fanlizhicyclopeptide A and fanlizhicyclopeptide B from plant exocarp showed anti-inflammatory activity by inhibition of the production of inflammatory mediators [52]. Moreover, cyclosquamosin D and cherimolacyclopeptide B from the seed extract inhibit the production of pro-inflammatory cytokines in activated macrophages [53, 54]. Additionally, they contribute to the cytotoxic activity of the plant such as annosquamosin A which has anti-cancer activity against 95-D lung cancer cells and A2780 ovarian cancer cells [49]. Moreover, cyclosquamosin B showed a vasorelaxant activity that is thought to be due to the inhibition of calcium influx by blocking of voltage-gated calcium channels [55]. **Table 4** shows some of the previously isolated Cyclic peptides from *A. squamosa*.

Table 4: Some of the previously isolated Cyclic peptides from *A. squamosa*

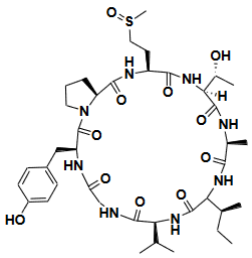
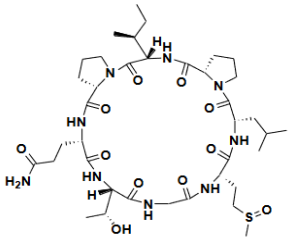
Name	Structure	Plant part
1 Annosquamosin A		Seed [56]
2 Cherimolacyclopeptide B		Seed [53]

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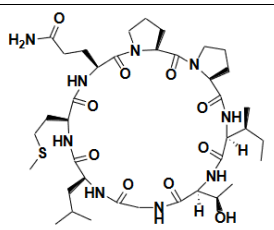
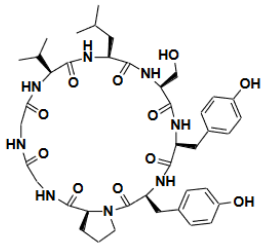
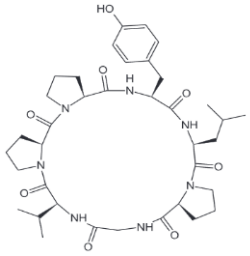
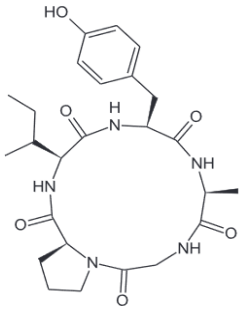
Table 4: Continue

3	Cyclosquamosin B		Seed [57]
4	Cyclosquamosin D		Seed [57]
5	Fanlizhicyclopeptide A		Exocarp [52]
6	Fanlizhicyclopeptide B		Exocarp [52]

4.5. Essential oils

The analysis of *A. squamosa* leaf essential oils showed that sesquiterpenes represent the majority of the oils. Germacrene D and bicyclogermacrene contribute with the largest percentage of oil composition with 17.1 % and 10.8 % respectively [58]. The pericarp essential oil with (-)-spathulenol (32.51%) as the major constituent showed cytotoxic activity against SMMC-7721 hepatoma cell line [59]. On the other hand, the bark essential oil containing 1H-cycloprop(e) azulene (3.46%), germacrene D (11.44%), bisabolene (4.48%), caryophyllene oxide (29.38%), bisabolene epoxide (3.64%) and kaur-16-ene (19.13%) as the major constituents with antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus* [60]. Also, caryophyllene oxide, which was isolated from the bark, has analgesic and anti-inflammatory activity [61]. **Table 5** shows some of the previously detected essential oil components from *A. squamosa*.

5. Biological and pharmacological activities of *A. squamosa*

A. squamosa is a medicinally active plant that is rich in many active constituents that can be effective for different health problems [65]. The different parts of the plant, seeds, leaves, and fruits, contribute to the pharmacological activities which include the following:

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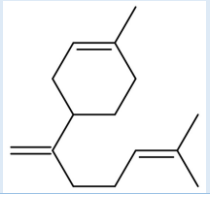
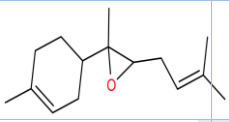
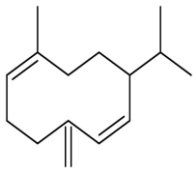
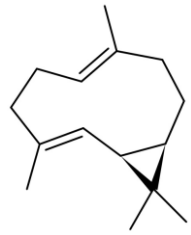
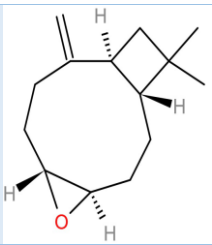
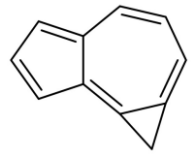
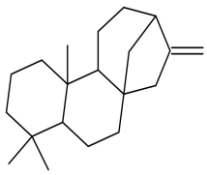
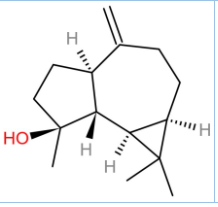
Table 5: Some of the previously isolated essential oil components from *A. squamosa*

	Name	Structure	Plant part
1	Bisabolene		Bark (60)
2	Bisabolene epoxide		Bark (60)
3	Germacrene D		Fruit pulp (62), bark (63)
4	Bicyclogermacrene		Fruit pulp (62), Leaves (64)
5	Caryophyllene oxide		Bark (63), Leaves (64)
6	1H-cycloprop (e) azulene		Bark (63)
7	Kaur-16-ene		Bark (63)
8	Spathulenol		Pericarp (59)

5.1.Anti-tumor activity

A. squamosa different extracts showed anticancer activity either against human cell lines or in animal models. The cytotoxic effect of the seed extract is mainly due presence of cytotoxic acetogenins that induce apoptosis and increase the production of free radicals in cancer cells [66]. *In vivo* study showed that both aqueous and organic seed extracts exhibited a potent cytotoxic activity against a rat histiocytic tumor cell line, AK-5 [67]. Another study was performed using the aqueous and organic seed extracts that showed promising activity against MCF-7 and K-562 cell lines [68]. The ethyl acetate fraction of seed ethanolic extract was studied to investigate its effect on hepatoma cell lines. The extract showed significant activity against Hep G2 cell lines. Additionally, the oral administration of the seed extract inhibited the growth of H_{22} tumor cells in mice [69]. Moreover, The leaf extract is found to be effective against T-cell leukemia/lymphoma [70]. The ethanolic leaf extract as well as the ethyl acetate fraction were reported to be effective against human epidermoid carcinoma cell line KB-3-1 and colon cancer cell line HCT-116 [71]. Recently, different extracts of *A. squamosa* leaves were tested against different breast cancer cell lines, MCF-7 and MDA-MB-231. The study showed that all extracts exhibited an antiproliferative effect and induced apoptosis in the two cell lines [72].

5.2. Anti-inflammatory activity

As *A. squamosa* extracts were reported to decrease the activity of inflammatory mediators, that play an important role in different inflammatory conditions [61, 73]. Methanolic leaf and bark extracts were revealed to exert a potent anti-inflammatory effect by reducing IL-6 secretion [73]. an *in vitro* study conducted on the ethanolic extract of fruit peel showed that the extract exhibited a strong anti-inflammatory effect in an induced rheumatoid arthritis mice model [74].

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Furthermore, the anti-inflammatory effect of aqueous leaf extract was evaluated using an experimental ulcerative colitis animal model. It was found that the extract decreased colonic malondialdehyde (MDA) and increased colonic glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT) activities [75]. The anti-inflammatory effect of leaf ethanolic extract was also confirmed by its ability to decrease carrageenan-induced edema in rat paws by about 47.16% [76]. One of the most interesting outcomes of the anti-inflammatory properties of *A. squamosa* is the anti-psoriatic effect of seed oil. Petroleum ether seed extract was evaluated *in vitro* and *in vivo* to evaluate this effect. It was observed that the antiproliferative effect of the seed extract was higher than that observed with topical clobetasol propionaste. The oil also showed a remarkable decrease in the inflammatory mediators responsible for most of the symptoms [77].

5.3. Antioxidant activity

A. squamosa leaf extract, with its content of flavonoids, glycosides, saponins, phenols, and tannins, has free radical scavenging properties [78]. The ethanolic leaf extract showed strong free radical scavenging activity [79]. Another *in vivo* study to evaluate the antioxidant activity of *A. squamosa* showed that the water leaf extract increased the activities of catalase, superoxide dismutase, reduced glutathione, glutathione reductase, and glutathione-s-transferase, which act as scavenging enzymes, and decreased malondialdehyde levels in different tissues [80]. ASPW80-1, a water-soluble polysaccharide isolated from *A. squamosa* pulp, has hydroxyl radical scavenging activity and can also proliferate the spleen cells [81]. Furthermore, the seed oil, with its tocopherol content, has significant antioxidant activity [82].

5.4. Antidiabetic activity

A. squamosa extracts from several organs, including seeds, leaves, and pulp, were reported to have hypoglycemic activity [83-85]. The leaf extract was found to enhance insulin secretion and inhibit *α*- glucosidase activity, which decreases blood sugar levels [84]. Additionally, the oral administration of alcoholic leaf extract was reported to decrease blood sugar levels in a non-insulin-dependent diabetes mellitus (NIDDM) rat model [86]. Moreover, the hexane leaf extract was used to detect the hypoglycemic mechanism of action of *A. squamosa*. The study revealed that the extract inhibited protein tyrosine phosphatase 1B (PTP1B), leading to insulin signalling modulation [87]. Also, GASP3-3-I, which is a polysaccharide isolated from the fruit pulp, has *α*-glucosidase inhibitory activity [88]. The combination of *A. squamosa* leaf extract and glipizide was reported to be effective in reducing the glipizide dose by 50% [89].

5.5. Antifungal and antimicrobial activity

The leaf extract was found to be effective against different fungal strains such as *Alternaria alternate, Candida albicans, Fusarium solani, Microsporum canis*, and *Aspergillus niger* [78]. *A. squamosa* leaf extract was reported to have antibacterial activity against both gram-positive and gram-negative bacteria. It has bactericidal activity against *Staphylococcus aureus*, and bacteriostatic activity against many species, such as *Klebsiella pneumoniae* and *Enterococcus faecalis* [90]. The fruit extract was tested for its antibacterial effect using saliva samples. The study showed that *A. squamosa* extract exhibited an antibacterial effect comparable to that of chlorhexidine [91]. Moreover, the methanolic seed extract was reported to exert strong activity against some gram-positive (*Bacillus subtilis, Staphylococcus aureus*) and gram-negative (*Escherichia coli, Pseudomonas aeruginosa,*

ISSN: 3009-7061

and *Klebsiella pneumoniae*) bacteria [92]. Another study, performed using fruit peel alcoholic extract, reported an antibacterial effect against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [93].

5.6.Hepatoprotective activity

The methanol extract of *A. squamosa* leaves and the hydroalcoholic extract of the seeds were reported to have a protective effect on liver cells [94, 95]. The leaf extract was found to restore elevated liver enzymes and bilirubin in chemically induced hepatotoxic rats [95]. The hepatoprotective effect of the hydroalcoholic seed extract was evaluated *in vivo* against carbon tetrachloride-induced hepatotoxicity. The study revealed that the seed extract exhibited a promising hepatoprotective effect demonstrated by reducing the levels of SGOT, SGPT, ALP, and total bilirubin [94].

5.7.Wound healing activity

The ethanolic extract of *A. squamosa* leaves was found to increase collagen synthesis and cell proliferation when applied topically, which may be helpful for wound healing [96]. In another study, the alcoholic extract of *A. squamosa* leaves was used topically to evaluate its wound-healing activity in streptozotocin-induced diabetic rats. The extract was found to promote wound healing by increasing DNA, protein, collagen, and cellular proliferation at the wound site [97].

Currently, *Annona* plants are receiving special attention for their potent effects in combating cancer. Researchers are particularly interested in the remarkable anti-cancer properties exhibited by various compounds found within *Annona* species [72, 73, 98]. Moreover, there is a notable increase in studies concerning the applications of nanoparticle drug delivery systems in combination with different *A. squamosa* extracts for different therapeutic purposes [99-101]. Also, there is an increasing interest in the promising antidiabetic effect of some *Annona* species [102-104]. All these make *A. squamosa* an optimal point for future investigations.

6. Conclusions

A. squamosa is a valuable plant species within the Annonaceae family, known for its diverse medicinal properties. The presence of acetogenins, alkaloids, diterpenes, and cyclopeptides contributes to its pharmacological activities. The identification and understanding of these active constituents provide insights into the potential therapeutic applications of *A. squamosa* in various health conditions. It is also observed that most of the studies have focused on the pharmacological activities of different plant extracts and isolated compounds, but the mechanism of action of these compounds is still not well studied. Additionally, further investigations of the possible toxicity of these compounds are required to provide a complete picture of their safety and efficacy. Furthermore, the nutritional value of *A. squamosa* can be an interesting point to study. Finally, this review article aims to be a source of inspiration and direction for conducting additional preclinical and clinical studies on the utilization of *A. squamosa* in clinical and pharmaceutical fields.

Competing interests

The authors declare no competing interests.

Author contributions

Safaa Yassin carried out the review and wrote the manuscript. Masouda E Amer suggested the review point. All authors reviewed the manuscript revision.

Acknowledgment

We extend our gratitude to all the reviewers of this article, whose efforts have significantly contributed to the enhancement of the quality of this review.

Highlights

- The review mentioned the recently isolated compounds from *A. squamosa*.
- The chemistry and biological activities of some isolated compounds were reviewed.

ISSN: 3009-7061

- The activities of *A. squamosa* total extracts from different parts were highlighted.

7. References

(1) Salmerón-Manzano E, Garrido-Cardenas JA, Manzano-Agugliaro F. Worldwide research trends on medicinal plants. International journal of environmental research and public health. 2020;17(10):3376.

(2) Pešić M, Stanković S. Development of natural product drugs in a sustainable manner. Brief for United Nations Global Sustainable Development Report. 2015.

(3) Bauer A, Brönstrup M. Industrial natural product chemistry for drug discovery and development. Natural product reports. 2014;31(1):35-60.

(4) Tsabang N, Fokou PVT, Tchokouaha LRY, Noguem B, Bakarnga-Via I, Nguepi MSD, et al. Ethnopharmacological survey of Annonaceae medicinal plants used to treat malaria in four areas of Cameroon. Journal of Ethnopharmacology. 2012;139(1):171-80.

(5) Aminimoghadamfarouj N, Nematollahi A, Wiart C. Annonaceae: bio-resource for tomorrow's drug discovery. Journal of Asian natural products research. 2011;13(05):465-76.

(6) Couvreur TL, Pirie MD, Chatrou LW, Saunders RM, Su YC, Richardson JE, et al. Early evolutionary history of the flowering plant family Annonaceae: steady diversification and boreotropical geodispersal. Journal of Biogeography. 2011;38(4):664-80.

(7) Couvreur TL, Helmstetter AJ, Koenen EJ, Bethune K, Brandão RD, Little SA, et al. Phylogenomics of the major tropical plant family Annonaceae using targeted enrichment of nuclear genes. Frontiers in plant science. 2019;9:1941.

(8) Badrie N, Schauss AG. Soursop (Annona muricata L.): composition, nutritional value, medicinal uses, and toxicology. Bioactive foods in promoting health: Elsevier; 2010. p. 621-43.

(9) Dahiya R, Dahiya S. Natural bioeffective cyclooligopeptides from plant seeds of Annona genus. European Journal of Medicinal Chemistry. 2021:113221.

(10) Pinto AdQ, Cordeiro MCR, De Andrade S, Ferreira FR, Filgueiras HdC, Alves R, et al. Annona species. Embrapa Cerrados-Livro científico (ALICE). 2005.

(11) Morton JF. Fruits of warm climates: JF Morton; 1987.

(12) Vyas K, Manda H, Sharma RK, Singhal G. An update review on Annona Squamosa. IJPT. 2012;3(2):107-18.

(13) Quílez AM, Fernández-Arche MA, García-Giménez MD, De la Puerta R. Potential therapeutic applications of the genus Annona: Local and traditional uses and pharmacology. Journal of Ethnopharmacology. 2018;225:244-70.

(14) Ma C-y, Chen Y, Chen J, Li X, Chen Y. A Review on Annona squamosa L.: Phytochemicals and Biological Activities. The American Journal of Chinese Medicine. 2017;45:1-32.

(15) Pellicciari C, Biggiogera M, Pellicciari. Histochemistry of single molecules: Springer; 2017.

(16) Kumar M, Changan S, Tomar M, Prajapati U, Saurabh V, Hasan M, et al. Custard apple (Annona squamosa L.) leaves: Nutritional composition, phytochemical profile, and health-promoting biological activities. Biomolecules. 2021;11(5):614.

(17) Moghadamtousi SZ, Fadaeinasab M, Nikzad S, Mohan G, Ali HM, Kadir HA. Annona muricata (Annonaceae): A Review of Its Traditional Uses, Isolated Acetogenins and Biological Activities. International Journal of Molecular Sciences. 2015;16(7):15625-58.

(18) Alali FQ, Liu X-X, McLaughlin JL. Annonaceous Acetogenins: Recent Progress. Journal of natural products. 1999;62(3):504-40.

(19) Zafra-Polo MC, Figadère B, Gallardo T, Tormo J, Cortes D. Natural acetogenins from Annonaceae, synthesis and mechanisms of action. Phytochemistry. 1998;48(7):1087-117.

(20) Liaw C-C, Liou J-R, Wu T-Y, Chang F-R, Wu Y-C. Acetogenins from annonaceae. Progress in the Chemistry of Organic Natural Products 101. 2016:113-230.

(21) Dang QL, Kim WK, Nguyen CM, Choi YH, Choi GJ, Jang KS, et al. Nematicidal and Antifungal Activities of Annonaceous Acetogenins from Annona squamosa against Various Plant Pathogens. Journal of Agricultural and Food Chemistry. 2011;59(20):11160-7.

(22) Oberlies NH, Jones JL, Corbett TH, Fotopoulos SS, McLAUGHLIN JL. Tumor cell growth inhibition by several Annonaceous acetogenins in an in vitro disk diffusion assay. Cancer letters. 1995;96(1):55-62.

(23) Mukhlesur Rahman M, Parvin S, Ekramul Haque M, Ekramul Islam M, Mosaddik MA. Antimicrobial and cytotoxic constituents from the seeds of Annona squamosa. Fitoterapia. 2005;76(5):484-9.

(24) Pathak J, Patel PK, Suthar R, Shah KR. Identification of Phytochemicals from seed extract of Custard Apple (Annona squamosa L.).

ISSN: 3009-7061

Biosci Biotechnol Res Commun. 2021;14:397-402.
(25) Carmen Zafra-Polo M, Figadère B, Gallardo T, Tormo J, Cortes D. Natural acetogenins from annonaceae, synthesis and mechanisms of action. Phytochemistry. 1998;48(7):1087-117.
(26) Miao Y, Xu X, Yuan F, Shi Y, Chen Y, Chen J, et al. Four cytotoxic annonaceous acetogenins from the seeds of Annona squamosa. Natural product research. 2016;30(11):1273-9.
(27) Liaw C-C, Yang Y-L, Chen M, Chang F-R, Chen S-L, Wu S-H, et al. Mono-tetrahydrofuran annonaceous acetogenins from Annona squamosa as cytotoxic agents and calcium ion chelators. Journal of natural products. 2008;71(5):764-71.
(28) Ma C, Wang Q, Shi Y, Li Y, Wang X, Li X, et al. Three new antitumor annonaceous acetogenins from the seeds of Annona squamosa. Natural product research. 2017;31(18):2085-90.
(29) Ma C, Li Y, Lu J, Wang M, Li X, Chen J, et al. Three new cytotoxic annonaceous acetogenins from the seeds of Annona squamosa. Natural Product Research. 2023.
(30) Cheng-Yao M, Jia-Hui L, Xiang L, Xiao L, Jian-Wei C. Eight new cytotoxic annonaceous acetogenins from the seeds of Annona squamosa. Chinese journal of natural medicines. 2019;17(4):291-7.
(31) Miao Y-J, Shi Y-Y, Xu X-F, Chen Y, Chen J-W, Li X. Three cytotoxic Annonaceous acetogenins from the seeds of Annona squamosa. Phytochemistry Letters. 2016;16:92-6.
(32) Bhardwaj R, Pareek S, Sagar N, Vyas N. Bioactive compounds of Annona. Bioactive compounds in underutilized fruits and nuts. 2020:37-62.
(33) Avula B, Bae J-Y, Majrashi T, Wu T-Y, Wang Y-H, Wang M, et al. Targeted and non-targeted analysis of annonaceous alkaloids and acetogenins from Asimina and Annona species using UHPLC-QToF-MS. Journal of pharmaceutical and biomedical analysis. 2018;159:548-66.
(34) Shami AM. The effect of alkaloidal fraction from Annona squamosa L. against pathogenic bacteria with antioxidant activities. Pharmaceutical Sciences. 2017;23(4):301-7.
(35) Al-ghazzawi AM. Anti-cancer activity of new benzyl isoquinoline alkaloid from Saudi plant Annona squamosa. BMC Chemistry. 2019;13(1):13.
(36) Vila-Nova NS, Morais SMd, Falcão MJC, Machado LKA, Beviláqua CML, Costa IRS, et al. Leishmanicidal activity and cytotoxicity of compounds from two Annonacea species cultivated in Northeastern Brazil. Revista da Sociedade Brasileira de Medicina Tropical. 2011;44:567-71.
(37) Johns T, Windust A, Jurgens TJ, Mansor S, editors. Antimalarial alkaloids isolated from Annona squamosa2011.
(38) Soni VK, Yadav DK, Bano N, Dixit P, Pathak M, Maurya R, et al. N-methyl-6, 7-dimethoxyisoquinolone in Annona squamosa twigs is the major immune modifier to elicit polarized Th1 immune response in BALB/c mice. Fitoterapia. 2012;83(1):110-6.
(39) Yadav DK, Singh N, Dev K, Sharma R, Sahai M, Palit G, et al. Anti-ulcer constituents of Annona squamosa twigs. Fitoterapia. 2011;82(4):666-75.
(40) Bhakuni DS, Tewari S, Dhar MM. Aporphine alkaloids of annona squamosa. Phytochemistry. 1972;11(5):1819-22.
(41) Johns T, Windust A, Jurgens T, Mansor SM. Antimalarial alkaloids isolated from Annona squamosa. Phytopharmacology. 2011;1(3):49-53.
(42) Jayendra, Kumar Y, Kumar SS. Two new tetrahydroisoquinoline analogs from Indian medicinal plant Annona squamosa. Journal of Pharmacy Research. 2013;7(6):510-5.
(43) Al-Ghazzawi AM. Anti-cancer activity of new benzyl isoquinoline alkaloid from Saudi plant Annona squamosa. BMC chemistry. 2019;13(1):1-6.
(44) Zhou CX, Sun LR, Feng F, Mo JX, Zhu H, Yang B, et al. Cytotoxic Diterpenoids from the Stem Bark of Annona squamosa L. Helvetica Chimica Acta. 2013;96(4):656-62.
(45) Joy B, Remani P. Antitumor constituents from Annona squamosa fruit pericarp. Medicinal Chemistry Research. 2008;17(2):345-55.
(46) Chen Y-y, Cao Y-z, Li F-q, Zhu X-l, Peng C-x, Lu J-h, et al. Studies on anti-hepatoma activity of Annona squamosa L. pericarp extract. Bioorganic & Medicinal Chemistry Letters. 2017;27(9):1907-10.
(47) Wu Y-C, Hung Y-C, Chang F-R, Cosentino M, Wang H-K, Lee K-H. Identification of ent-16β,17-Dihydroxykauran-19-oic Acid as an Anti-HIV Principle and Isolation of the New Diterpenoids Annosquamosins A and B from Annona squamosa. Journal of natural products. 1996;59(6):635-7.
(48) Yang Y-L, Chang F-R, Wu C-C, Wang W-Y, Wu Y-C. New E Nt-Kaurane Diterpenoids with Anti-Platelet Aggregation Activity from Annona s Quamosa. Journal of natural products. 2002;65(10):1462-7.
(49) Sun L, Zhu H, Gan L, Mo J, Feng F, Zhou C. Constituents from the bark of Annona squamosa

ISSN: 3009-7061

and their anti-tumor activity. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica. 2012;37(14):2100-4.
(50) Yang Y-L, Chang F-R, Hwang T-L, Chang W-T, Wu Y-C. Inhibitory effects of ent-kauranes from the stems of Annona squamosa on superoxide anion generation by human neutrophils. Planta medica. 2004;70(03):256-8.
(51) Joo SH. Cyclic peptides as therapeutic agents and biochemical tools. Biomolecules & therapeutics. 2012;20(1):19-26.
(52) Wu P, Wu M, Xu L, Xie H, Wei X. Anti-inflammatory cyclopeptides from exocarps of sugar-apples. Food chemistry. 2014;152:23-8.
(53) Yang Y-L, Hua K-F, Chuang P-H, Wu S-H, Wu K-Y, Chang F-R, et al. New cyclic peptides from the seeds of Annona squamosa L. and their anti-inflammatory activities. Journal of agricultural and food chemistry. 2008;56(2):386-92.
(54) Dellai A, Maricic I, Kumar V, Arutyunyan S, Bouraoui A, Nefzi A. Parallel synthesis and anti-inflammatory activity of cyclic peptides cyclosquamosin D and Met-cherimolacyclopeptide B and their analogs. Bioorganic & medicinal chemistry letters. 2010;20(19):5653-7.
(55) Morita H, Iizuka T, Choo C-Y, Chan K-L, Takeya K, Kobayashi Ji. Vasorelaxant activity of cyclic peptide, cyclosquamosin B, from Annona squamosa. Bioorganic & medicinal chemistry letters. 2006;16(17):4609-11.
(56) Li C-M, Tan N-H, Mu Q, Zheng H-L, Hao X-J, Wu Y, et al. Cyclopeptide from the seeds of Annona squamosa. Phytochemistry. 1997;45(3):521-3.
(57) Morita H, Sato Y, Kobayashi Ji. Cyclosquamosins A–G, cyclic peptides from the seeds of Annona squamosa. Tetrahedron. 1999;55(24):7509-18.
(58) Costa E, Meira C, Guimaraes E, Macedo T, Silva T, Menezes L, et al. Chemical composition of essential oils from Annona vepretorum Mart. and Annona squamosa L. (Annonaceae) leaves and their antimalarial and trypanocidal activities. Journal of Essential Oil Research. 2015;27.
(59) Chen Y-Y, Peng C-X, Hu Y, Bu C, Guo S-C, Li X, et al. Studies on chemical constituents and anti-hepatoma effects of essential oil from Annona squamosa L. pericarps. Natural Product Research. 2017;31(11):1305-8.
(60) Chavan MJ, Shinde DB, Nirmal SA. Major volatile constituents of Annona squamosa L. bark. Natural Product Research. 2006;20(8):754-7.
(61) Chavan M, Wakte P, Shinde D. Analgesic and anti-inflammatory activity of Caryophyllene oxide from Annona squamosa L. bark. Phytomedicine. 2010;17(2):149-51.
(62) Andrade EHA, Maria das Graças BZ, Maia JGS, Fabricius H, Marx F. Chemical characterization of the fruit of Annona squamosa L. occurring in the Amazon. Journal of Food Composition and Analysis. 2001;14(2):227-32.
(63) Chavan M, Shinde D, Nirmal S. Major volatile constituents of Annona squamosa L. bark. Natural product research. 2006;20(8):754-7.
(64) Verma R, Joshi N, Padalia R, Singh V, Goswami P. Characterization of the leaf essential oil composition of Annona squamosa L. from foothills of north India. Med Aromat Plants (Los Angel). 2016;5(270):2167-0412.1000270.
(65) Oo WM, Khine MM. Pharmacological Activities of Annona squamosa: Updated. Chemistry. 2017;3(6):86-93.
(66) Pardhasaradhi B, Reddy M, Ali AM, Kumari AL, Khar A. Differential cytotoxic effects ofAnnona squamosa seed extracts on human tumour cell lines: role of reactive oxygen species and glutathione. Journal of biosciences. 2005;30(2):237-44.
(67) Pardhasaradhi B, Reddy M, Ali AM, Kumari AL, Khar A. Antitumour activity of Annona squamosa seed extracts is through the generation of free radicals and induction of apoptosis. 2004.
(68) Pardhasaradhi BVV, Reddy M, Ali AM, Kumari AL, Khar A. Differential cytotoxic effects ofAnnona squamosa seed extracts on human tumour cell lines: Role of reactive oxygen species and glutathione. Journal of Biosciences. 2005;30(2):237-44.
(69) Chen Y, Xu S-s, Chen J-w, Wang Y, Xu H-q, Fan N-b, et al. Anti-tumor activity of Annona squamosa seeds extract containing annonaceous acetogenin compounds. Journal of Ethnopharmacology. 2012;142(2):462-6.
(70) Nakano D, Ishitsuka K, Kamikawa M, Matsuda M, Tsuchihashi R, Okawa M, et al. Screening of promising chemotherapeutic candidates from plants against human adult T-cell leukemia/lymphoma (III). Journal of natural medicines. 2013;67(4):894-903.
(71) Wang D-S, Rizwani GH, Guo H, Ahmed M, Ahmed M, Hassan SZ, et al. Annona squamosa Linn: cytotoxic activity found in leaf extract against human tumor cell lines. Pak J Pharm Sci. 2014;27(5):1559-63.
(72) Al-Nemari R, Bacha AB, Al-Senaidy A, Almutairi MH, Arafah M, Al-Saran H, et al. Cytotoxic effects of Annona squamosa leaves against breast cancer cells via apoptotic

ISSN: 3009-7061

signaling proteins. Journal of King Saud University - Science. 2022;34(4):102013.
(73) Awada N, Ayoub A, Jaber A, Ibrahim F, El Ghotmi N, Cheble E. Evaluation of the Anticancer, Anti-Inflammatory, and Antioxidant Properties of Various Extracts of Annona squamosa L.. Pharm Sci. 2023;29(3):384-94.
(74) Nguyen TT, Tran PNT, Phan HT. Evaluation of anti-inflammatory effect of fruit peel extracts of Annona squamosa L. on mouse models of rheumatoid arthritis. Journal of microbiology, biotechnology and food sciences. 2021;11(2):e2075-e.
(75) Ibrahim RY, Hassan AI, Al-Adham EK. The anti-ulcerative colitis effects of Annona squamosa Linn. leaf aqueous extract in experimental animal model. International journal of clinical and experimental medicine. 2015;8(11):21861.
(76) Singh DP, Mishra B, Mishra R. Anti-nociceptive and anti-inflammatory activity of Annona squamosa L. leaf extract in mice and rats. Research Journal of Pharmacognosy and Phytochemistry. 2012;4(3):182-5.
(77) Bhoir SS, Vishwapathi V, Singh KK. Antipsoriatic potential of Annona squamosa seed oil: An in vitro and in vivo evaluation. Phytomedicine. 2019;54:265-77.
(78) Kalidindi N, Thimmaiah NV, Jagadeesh NV, Nandeep R, Swetha S, Kalidindi B. Antifungal and antioxidant activities of organic and aqueous extracts of Annona squamosa Linn. leaves. Journal of food and drug analysis. 2015;23(4):795-802.
(79) Shirwaikar A, Rajendran K, Kumar CD. In vitro antioxidant studies of Annona squamosa Linn. leaves. 2004.
(80) Gupta RK, Kesari AN, Diwakar S, Tyagi A, Tandon V, Chandra R, et al. In vivo evaluation of anti-oxidant and anti-lipidimic potential of Annona squamosa aqueous extract in Type 2 diabetic models. Journal of Ethnopharmacology. 2008;118(1):21-5.
(81) Tu W, Zhu J, Bi S, Chen D, Song L, Wang L, et al. Isolation, characterization and bioactivities of a new polysaccharide from Annona squamosa and its sulfated derivative. Carbohydrate polymers. 2016;152:287-96.
(82) Luzia DMM, Jorge N. Soursop (Annona muricata L.) and sugar apple (Annona squamosa L.): Antioxidant activity, fatty acids profile and determination of tocopherols. Nutrition & Food Science. 2012.
(83) Sangala R, Kodati D, Burra S, Gopu J, Dubasi A. Evaluation of antidiabetic activity of Annona squamosa Linn Seed in alloxan–induced diabetic rats. Diabetes. 2011;2(1):100-6.
(84) Tripathi YB. Insulin secreting and α-glucosidase inhibitory activity of hexane extract of Annona squamosa Linn. in streptozotocin (STZ) induced diabetic rats. 2014.
(85) Gupta RK, Kesari AN, Watal G, Murthy P, Chandra R, Tandon V. Nutritional and hypoglycemic effect of fruit pulp of Annona squamosa in normal healthy and alloxan-induced diabetic rabbits. Annals of nutrition and Metabolism. 2005;49(6):407-13.
(86) Shirwaikar A, Rajendran K, Kumar C. Oral Antidiabetic Activity of Annona squamosa Leaf Alcohol Extract in NIDDM Rats. Pharmaceutical Biology. 2004;42(1):30-5.
(87) Davis JA, Sharma S, Mittra S, Sujatha S, Kanaujia A, Shukla G, et al. 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(3):326-32.
(88) Ren Y-y, Zhu Z-Y, Sun H-q, Chen L-J. Structural characterization and inhibition on α-glucosidase activity of acidic polysaccharide from Annona squamosa. Carbohydrate Polymers. 2017;174:1-12.
(89) Kaur R, Afzal M, Kazmi I, Ahamd I, Ahmed Z, Ali B, et al. Polypharmacy (herbal and synthetic drug combination): a novel approach in the treatment of type-2 diabetes and its complications in rats. Journal of Natural Medicines. 2013;67(3):662-71.
(90) Pinto NCC, Silva JB, Menegati LM, Guedes M, Marques LB, Silva TPD, et al. Cytotoxicity and bacterial membrane destabilization induced by Annona squamosa L. extracts. An Acad Bras Cienc. 2017;89(3 Suppl):2053-73.
(91) Ali SH, Jafar ZJ. Comparison of Antibacterial Efficacy of Annona Squamosa Mouthwash with Chlorhexidine for Children. J Res Med Dent Sci. 2022;10:87-94.
(92) Aher P, Shinde Y, Chavan P. In vitro evaluation of antibacterial potential of Annona squamosa L. against pathogenic bacteria. International Journal of Pharmaceutical Sciences and Research. 2012;3(5):1457-60.
(93) Altaee MF, Younis R, Kamona Z. ACTIVITY OF Annona Squamosa PEELS EXTRACTS AGAINST TWO PATHOGENIC BACTERIA AND TWO BLOOD CANCER CELL LINES. Iraqi Journal of Agricultural Sciences. 2020;51(6).
(94) Mehta SD, Paliwal S. Hepatoprotective activity of hydroalcohilic extract of Annona squamosa seeds. Int J Pharm Phyto Res. 2017;9:997-1000.

ISSN: 3009-7061

(95) Raj DS, Vennila JJ, Aiyavu C, Panneerselvam K. The hepatoprotective effect of alcoholic extract of Annona squamosa leaves on experimentally induced liver injury in Swiss albino mice. International Journal of Integrative Biology. 2009;5(3):182-6.
(96) Ponrasu T, Suguna L. Efficacy of Annona squamosa L in the synthesis of glycosaminoglycans and collagen during wound repair in streptozotocin induced diabetic rats. BioMed research international. 2014;2014.
(97) Ponrasu T, Suguna L. Efficacy of Annona squamosa on wound healing in streptozotocin-induced diabetic rats. International wound journal. 2012;9(6):613-23.
(98) Swantara MD, Rita WS, Dira MA, Agustina KK. Cervical anticancer activities of Annona squamosa Linn. leaf isolate. Veterinary World. 2022;15(1):124.
(99) Mohamad EA, Abdellatif KK, Maihop DI, Abdelmonaem DM, Bahaa-aldine F, Abdelkhaliq AE. Antitumor efficacy of Annona squamosa loaded niosomes. BioNanoScience. 2023;13(4):2225-31.
(100) Mokhtar FA, Selim NM, Elhawary SS, Abd El Hadi SR, Hetta MH, Albalawi MA, et al. Green Biosynthesis of Silver Nanoparticles Using Annona glabra and Annona squamosa Extracts with Antimicrobial, Anticancer, Apoptosis Potentials, Assisted by In Silico Modeling, and Metabolic Profiling. Pharmaceuticals. 2022;15(11):1354.
(101) Malik M, Iqbal MA, Malik M, Raza MA, Shahid W, Choi JR, et al. Biosynthesis and Characterizations of Silver Nanoparticles from Annona squamosa Leaf and Fruit Extracts for Size-Dependent Biomedical Applications. Nanomaterials. 2022;12(4):616.
(102) Ansari P, Hannan JMA, Seidel V, Abdel-Wahab YHA. Polyphenol-Rich Leaf of Annona squamosa Stimulates Insulin Release from BRIN-BD11 Cells and Isolated Mouse Islets, Reduces (CH2O)n Digestion and Absorption, and Improves Glucose Tolerance and GLP-1 (7-36) Levels in High-Fat-Fed Rats. Metabolites. 2022;12(10):995.
(103) Alkhalidy H, Al-Nabulsi A, Mhawish R, Liu D. Low-dose of phenolic rich extract from Annona squamosa Linn leaves ameliorates insulin sensitivity and reduces body weight gain in HF diet-induced obesity. Front Nutr. 2023;10.
(104) Ponce-Sánchez C, Oidor-Chan VH, Álvarez-Ramírez EL, Gómez-Cansino R, Zarza-García AL, Gómez-Olivares JL, et al. Chemical profile and study of the antidiabetic effect of Annona squamosa L. peel. Waste and Biomass Valorization. 2023:1-11.

ISSN: 3009-7061