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Review

Chemopreventive Potential of Oils Extracted from Seeds of Three *Annona* Species

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Abstract: Annona fruit, leaves, seeds, roots, and bark have been conventionally used in many countries for medical treatments as they are considered ideal sources of pharmacologically active compounds, but Annona remains an underutilized fruit in many countries. The fruit of these plants is delicately flavored and is used in industrial products such as ready-to-serve beverages, wine, jellies, jam, and fruit-butter preserve, while the seeds generally go to waste. Annona seed oil contains numerous health-benefiting factors such as vitamins, minerals, bioactive compounds, fatty acids, antioxidants, and phenolic compounds, which are responsible for various biological activities, including antibacterial, antioxidant, and antitumor activities. Cancer is a worldwide major health problem that remains unresolved. Even though the current treatments can manage to reduce tumor growth, there is an urgent need to investigate more efficient but less expensive novel techniques to overcome some of the restrictions in treating tumors. Annona might offer an indispensable choice besides chemotherapy and radiotherapy, especially for terminally ill patients, as the Annona genus contains secondary metabolites in nearly every component of Annona plants. Research has shown that many *Annona* species contain promising components that could potentially exhibit anticancer activity, but the information available is scarce and inconsistent. *Annona muricata* (Soursop, "Katuanoda"), *Annona squamosa* (Sweetsop, "Seenianoda"), and *Annona reticulata* (Custard apple, "Welianoda") are three commonly cultivated edible *Annona* species in Sri Lanka. The main objective of the review was to present an updated comprehensive literature analysis of the putative chemopreventive functions against cancer cell lines/the anticancer effect on cancers, phytochemical properties, and antioxidant properties possessed by the seed oils of three selected common *Annona* species. Although there are some in vitro and in vivo experimental investigations supporting the benefits of Annona seed oils, clinical investigations are still needed to explore concealed areas, determine the effects on the human body, determine the safest concentration, and determine health-contributing benefits before they are submitted to clinical trials.

Keywords: *Annona muricata*; *Annona squamosa*; *Annona reticulata*; Annona seed oil; antioxidants; chemopreventive potential; phytochemicals

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1. Introduction

Annona is considered an important yet underutilized fruit with high nutritional and medicinal value [1]. These different plant-based medicinal compounds are prepared using a variety of different procedures, including infusions, pastes, and decoctions, in traditional remedies [2–4]. In particular, *Annona reticulata* bark, root bark, and root decoction are used for toothache, fever, and, as an antipyretic and immature fruit, for the treatment of dysentery and diarrhea. In addition, *Annona squamosa* and *Annona muricata* have been recorded for their antidiarrheal effects, and their leaves are used to make tea to treat colic; leaf decoction has been used to treat worms, boils, and abscesses; and seed paste is used to treat cancer and heal cattle wounds [5–8]. Regarding *A. muricata*, its dried leaves are used to treat spasms and dysentery and taken orally for analgesic effects in certain regions of Indonesia, and its fruit juice is used as a diuretic and to treat liver disorders [8–11]. According to ethnobotanical studies, *A. muricata* seeds are toxic, yet the powder made from toasted seeds has been employed in traditional Mexican medicine [10]. In tropical America and India, the leaves of *A. squamosa* have been used systemically to treat dysentery as a tonic and cold medication [11]. *Annona cherimola*, *A. squamosa*, and *A. reticulata* have been documented for their antiparasitic properties. *A. muricata* and *Annona glabra* have also historically been utilized for curing rheumatism [12] while also being used to treat ulcers [13]. The leaves of *Annona diversifolia* have been utilized as analgesic, anticonvulsant, and anti-inflammatory medications [14].

Various studies have reported a variety of pharmacological activities, including antibacterial, anticancer, antidiarrhea, antidiabetic, anti-inflammatory, antioxidant, and antiulcer, that are attributed to the most abundant component vitamins, minerals, bioactive compounds, fatty acids (FAs), antioxidants, etc., of either crude extracts or isolated compounds from various parts of Annona species, especially leaves and seeds [2,15–23]. Among the 30 reviewed *Annona* species, six species, *A. squamosa*, *A. muricata*, *A. cherimola*, *A. senegalensis*, *A. reticulata*, and *A. coriacea*, are the most widely studied for their pharmacological activities and the phytochemical profiles of their bark, leaves, fruits, and seeds. For example, the leaf extracts of both *A. squamosa* and *A. reticulata* exhibited potent antiproliferative effects [24], and the ethanolic extract of *A. muricata* leaves was reported for its cytotoxicity against promonocytic leukemic cells [25]. Isocoreximine isolated from *A. cherimola* demonstrated cytotoxicity against multiple cancer cell lines, including the breast cancer cell line, the human colorectal carcinoma cell line, the human prostate tumor cell line, and the human leukemia cell line [26]. Additionally, various parts of *A. muricata*, including its bark, leaves, and stems, were shown to exhibit antioxidant activity using a DPPH assay [22], and the ethanolic extract of *A. squamosa* leaves was also reported to have antioxidant activity [27]. With regard to the phytochemistry of *Annona* species, alkaloids are mainly present in the leaves, whereas acetogenins are present in the seeds and found in smaller quantities in the pulp and leaves [28,29].

Annona fruit flesh is edible and is currently used in industrial products such as ready-to-serve beverages, wine, jellies, jam, and fruit butter preserve. These industries usually generate a considerable number of seeds as waste, and a renewed focus on the utilization of these wastes in food processing could minimize the accumulation of waste while concurrently contributing to minimizing the waste disposal problem and generating extra revenue [30]. Similarly, seed oils of edible fruits are important common food ingredients, and evidence has suggested that some compounds available in seeds may play different roles in human health, especially in acute and chronic disease management, such as cancer, cardiovascular diseases, and diabetes [31].

Cancer is a worldwide major health problem that remains unresolved, and the incidence of cancer is rising each year [32,33]. According to data from Cancer Research UK, there are more than 8 million cancer-related deaths every year in the world, and it is predicted that this figure will rise to 14.6 million by 2035 [34,35]. Cancer is a hereditary condition that develops when our bodies' genes, which regulate cell functions, growth, reproduction, and death, experience alterations [36]. The right cancer treatment, includ-

ing surgery, radiotherapy, chemotherapy, hormone treatments, and targeted biological therapies, depends on a proper cancer diagnosis. Concerns about the effectiveness of the current treatment options have been raised due to the prevalence and severity of cancer, which has led patients to search for alternatives that can complement or substitute the current treatment options [36,37]. There is an urgent need to investigate new techniques to overcome some of the restrictions in treating tumors, even though the current treatments can manage to reduce tumor growth [38].

Research has shown that many *Annona* species contain promising components that could potentially exhibit anticancer activity [39]. It has been decided to focus on three common *Annona* species, *A. muricata*, *A. squamosa*, and *A. reticulata*, since available evidence suggests that their uses and importance may be expanded, but the information available is scarce and inconsistent. Consequently, academics, researchers, extension workers, and farmers need better information [40]. A relationship between Annona's potential as an industrial pharmaceutical and a food supplement was established in the current investigation. As this notion has not yet been much revealed, an updated summary of the putative chemopreventive functions of Annona seed oils is provided in this review, along with a critical evaluation of the cytotoxicity activity against cancer cell lines, phytochemical properties, and antioxidant properties possessed by the seed oils of the three selected common *Annona* species.

2. Annona Genus

The family Annonaceae, which includes a variety of aromatic trees, bushes, shrubs, and climbers or lianas, includes the genus Annona. A few of these plants grow in temperate zones, although they are mostly found in tropical and subtropical areas [40,41]. Annona is the most significant genus in the Annonaceae family due to its edible fruits and therapeutic benefits [42]. The Latin word "anon," which means "yearly produce" and refers to the production of fruits from approximately 119 species globally, is the source of the genus name "Annona" [43,44]. Despite Annona having many species, only limited species of this family are economically important and commonly found in Sri Lanka, such as *A. squamosa* (sugar apple); *A. cherimola* (cherimoya); *A. muricata* (soursop); Atemoya, a hybrid between *A. cherimola* and *A. squamosa*; *A. reticulata* (Custard apple); and *A. glabra* (pond apple) [40,45]. There are many shared traits, and the species can be distinguished based on the traits of the plant, such as fruit size, shape, color, and quality, among others [46].

According to the Department of Agriculture, Sri Lanka, six edible *Annona* species can be commonly found in Sri Lanka, namely *A. muricata*, *A. squamosa*, *A. reticulata*, *A. glabra*, *A. cherimola*, and Atemoya (Figure 1) (Table 1) [40,45,47].

Among these, three species are commercially cultivated in Sri Lanka: *A. muricata*, *A. reticulata, and A. squamosa* [48].

A. muricata *A. reticulata* *A. squamosa*

Figure 1. Common *Annona* spp. grown in Sri Lanka.

Table 1. Commonly found Anonna species in Sri Lanka.

Botanical Name	Vernacular Name	Common Name
Annona muricata L.	Katuanoda	Soursop
Annona reticulata L.	Welianoda	Bullock's heart, custard apple
Annona squamosa L.	Sinianoda	Sweetsop/sugar apple
Annona cherimola Miller	Cherimoya	Cherimoya
A cross of *A. cherimola* and *A. squamosa*	Atemoya	Pineapple sugar apple
Annona glabra L.	Welatha	Pond apple, alligator apple

2.1. Annona muricata (Soursop)

A. muricata is called soursop in English, 'Katu anoda' in Sinhalese, and 'Sitha palam' in Tamil. It is probably indigenous to the West Indies and is grown in Sri Lanka's lowlands in wet zones [49]. It is a small tree, about 4–10 m tall, and its fruit are ovoid or irregularly ovoid, conical heart-shaped, dark green in color, and covered with soft spines (Figure 1). The fruit resembles white, less sweet, more acidic, cottony/fibrous, and juicy flesh and is used commercially for the production of candy, juice, and sherbets. It contains 127–170 blackish-brown seeds, which later turn brown during storage and are about 1–2 cm in size (Figure 2) [50–52]. This is the widely available *Annona* species in Sri Lanka, and several *A. muricata* accessions have been identified within the different agro-climatic zones in Sri Lanka. Most of the plant's parts have historically been used to treat a variety of illnesses, such as fever, rheumatism, and cancer [53]. Presently, individuals with cancer frequently utilize this plant, and numerous studies concentrate on the dietary, therapeutic, and bioactive components of *A. muricata* leaves [5].

Figure 2. General appearance of *A. muricata*, *A. squamosa*, and *A. reticulata* seeds (Scale 4:3).

2.2. Annona reticulata (Bullock's Heart/Custard Apple)

A. reticulata is named bullock's heart/custard apple in English, 'Welianoda' in Sinhalese, and 'Ramsitha' in Tamil. It originated in the West Indies and is grown as a fruit in Sri Lankan wet-zone home gardens. It has a small tree height of about 5–10 m, and the fruit is spherical, ovoid or heart-shaped, reddish-yellow, and possesses impressed lines above the carpels (Figure 1) [54]. For the treatment of epilepsy, diarrhea, cardiac issues, constipation, bleeding, bacterial infections, parasite and worm infestations, fever, ulcers, and as a pesticide, this plant's many parts are used in traditional medicines. There are frequently more than 40 black-brown, compacted, and glossy seeds about 1 cm in size (Figure 2) in its thick, cream-white flesh, and it has a somewhat granular body [55,56].

2.3. Annona squamosa (Sugar Apple/Sweetsop)

A. squamosa is called sugar apple/sweetsop in English, 'Sinianoda' in Sinhalese, and 'Sittapan' in Tamil and originated in tropical America and the West Indies. It is cultivated in Sri Lankan home gardens in low- and mid-country wet zones. It has a small tree, about 3–8 m high, with globular, cordate-ovoid, conical, or heart-shaped, yellowish-green fruit, which contains white pulp, which is pleasant, sweet–sour-flavored (Figure 1). The seeds are brownish black, about 1 cm in size (Figure 2), and each fruit contains about 35–45 [55,57]. This *Annona* species remains one of the most researched in the world and is well known for

having antidiabetic effects [58]. It has a variety of pharmacological characteristics, primarily antitumor properties, in its seeds, bark, and leaves [59].

3. Proximate Composition of Annona Seeds and Seed Oil Extraction

The impact of seed oil on human health is determined by its chemical composition. The proximate composition of *A. muricata*, *A. squamosa*, and *A. reticulata* seeds on a dry basis (g/100 g dry weight (DW) (%)) is summarized in Table 2.

Generally, Annona seeds are mainly composed of about 32.4% seed coat and 67.7% seed kernel. A proximate composition analysis of *A. muricata* seeds demonstrated the presence of 40% lipids, where *A. squamosa* seeds contain about 26.8% lipids, and *A. reticulata* seeds reveal the presence of 30.34% lipids g/100 g dry weight (DW) (%) [60–65]. These seeds have special potential for industrial use because of their high oil contents. The oil yield from seeds varies depending on the variety, seed size and shape, stage of fruit ripening, timing of seed harvest, soil and environmental conditions around the oil-bearing plant, pre-treatment procedure, and the particular extraction method used [60].

Table 2. The proximate analysis of seeds of *A. muricata*, *A. squamosa*, and *A. reticulata*.

Parameter (% g/100 g Dry Weight)	*A. muricata* *	*A. squamosa* **	*A. reticulata* ***
Moisture	7.7 ± 0.24	6.7 ± 0.2	15.2 ± 0.02
Lipid	40 ± 0.82	26.8 ± 0.4	30.34 ± 0.04
Protein	8.5 ± 0.52	17.5 ± 0.2	17.12 ± 0.01
Ash	9.7 ± 0.12	2.2 ± 0.1	4.5 ± 0.00
Fiber	5.2 ± 0.26	16.8 ± 0.2	32.0 ± 0.01
Carbohydrate (By Difference)	34.1	30.0	37.91

(* Onimawo [63]; ** Abdalbasit et al. [64]; *** Ezekiel et al. [65]).

Palm and olive oils are extracted from their fruits, and most vegetable oils such as cotton, sesame, ground nut, rape, corn, soya bean, and sunflower are extracted from seeds. According to the findings, seed oils can be extracted either by conventional extraction methods, such as solvent extraction, steam distillation, and mechanical pressing, or by non-conventional extraction methods, such as supercritical fluid extraction, pressurized liquid extraction, microwave-assisted extraction, ultrasound extraction, and pulsed electric field extraction. In fact, conventional methods are technically and scientifically challenging to handle and non-environmentally friendly [66–68], and until recently, the majority of reported seed oil extractions have been performed by Soxhlet extraction or cold pressing. The difference in oil content between these two extraction methods was not significant. This can be attributed to the possibility that during Soxhlet extraction, sample heating from the high temperature used for solvent evaporation may have caused oil droplets to emerge from the sample more readily; thus, the percentage of oil recovery from the seeds is high [61,69]. Though the majority of fruit seed oils are made by cold pressing the seeds, there are some instances where the oil content of the seeds is too low for cold pressing [70]. Regarding Annona seed oil (ASO), the maximally efficient extraction method has been shown to be Soxhlet extraction [68]. In Soxhlet extraction, the oils from the powdered seeds are extracted exhaustively with petroleum analytical-grade ether (boiling point: 60–80 °C) as the extraction solvent in the Soxhlet apparatus for 16 h, and the petroleum ether is separated from the oil by distillation at 100 °C in an air oven for 1 h [71].

Methyl esters of ASO have been studied using the GC/MS (gas chromatography–mass spectroscopy) method to determine their chemical composition. According to Table 3, oleic acid, linoleic acid, palmitic acid, and stearic acid were present in higher amounts, respectively, in all three ASO varieties, while linolenic acid, palmitoleic acid, myristic acid, and capric acid were found in trace amounts. Oleic acid was the most dominant FA (fatty acid), and linoleic acid was the second most dominant FA [63,72]. Further analyses of the *A. squamosa* seed oil (ASSO) revealed a significant concentration of UFAs (unsaturated fatty acids), and the linoleic and oleic acids provided about 70.3% of the total [63,73]. Even

within the same species, there may be variations in the FA composition of the seed oil. For instance, research revealed that oleic (37.0%), palmitic (25.1%), and linoleic (10.9%) acids were the predominant FAs in ASSO [74–76]. In contrast, 32.0% linoleic and 29.0% oleic contents have been observed [60]. Numerous studies have examined the chemical composition of ASSO, which was mostly found to be made up of oleic acid, linoleic acid, stearic acid, and palmitic acid, with UFAs composing up to approximately 70% of this mixture [77].

Table 3. The fatty acid composition of *A. muricata*, *A. squamosa*, and *A. reticulata* seeds, soybean, rapeseed, and sunflower.

Compound (%)	*A. muricata* seeds *	*A. squamosa* seeds **	*A. reticulata* seeds ***	Soybean *****	Rapeseed ****	Sunflower seed *****
Saturated fatty acids (SFA)						
Capric acid (10:0)	Traces	0.17 ± 0.03	Traces	-	-	-
Myristic acid (14:0)	Traces	0.67 ± 0.01	0.35 ± 0.03	0.10 ± 0.001	0.1	0.10 ± 0.003
Palmitic acid (C16:0)	20.41 ± 1.58	15.47 ± 0.17	14.1 ± 0.13	11.33 ± 0.56	3.49	6.94 ± 0.14
Stearic acid (C18:0)	4.13 ± 0.29	8.14 ± 0.04	6.86 ± 0.02	4.55 ±0.19	0.85	5.90 ± 0.10
Unsaturated fatty acids (UFA)						
Monounsaturated fatty acids (MUFA)						
Palmitoleic acid (C16:1)	1.44 ± 0.45	1.43 ± 0.03	1.41 ± 0.01	0.1	0.2	0.2
Oleic acid (C18: 1)	41.29 ± 0.53	48.54 ± 0.13	47.4 ± 0.01	22.24 ± 0.28	64.40	19.49 ± 0.76
Polyunsaturated fatty acids (PUFA)						
Linoleic acid (C18:2)	30.85 ± 0.34	23.40 ± 0.06	22.9 ± 0.03	54.67 ± 0.98	22.30	64.87 ± 1.94
Linolenic acid (C18:3)	1.88 ± 0.25	2.18 ± 0.03	1.79 ± 0.03	6.07 ± 0.17	8.23	1.90 ± 0.06
Total SFAs	24.54	24.45	24.35			
Total U FAs	75.46	75.55	75.65			

Values are mean ± SD for triplicate determinations. (* Kimbonguila et al. [78]; ** Abdalbasit et al. [63]; *** Abdalbasit et al. [63], Omkaresh et al. [72]; **** Ma and Hana. [79]; ***** Talpur et al. [80]; Kalo; and Kemppinen [81]).

Annona muricata seed oil (AMSO) contained SFAs (saturated fatty acids) and UFAs: 24.54% and 75.46%, respectively. Since it prevents heart problems, linoleic acid is one of the most significant PUFAs (polyunsaturated fatty acids) in human nutrition [82]. By using the Blye and Dyer method, 2.38% linolenic acid is recorded, and by using the Soxhlet method, 1.88% is recorded. Additionally, the Blye and Dyer method yields 1.20% palmitoleic acid, and the Soxhlet method yields 1.44%. Comparing the fatty acid composition of AMSO to that of vegetable oils reveals that this plant is particularly high in oleic acid, linoleic acid, and palmitic acid [78].

The amount of UFAs in *Annona reticulata* seed oil (ARSO) comprised a substantial amount of the total discovered FAs (75.65%), making the oil nutritionally desirable, while the proportion of SFAs was only 24.35% [72]. Research data on ARSO were rare, though it has been used commonly for indigenous medicinal purposes; thus, there is huge research potential.

4. Chemopreventive Agents of Annona Seed Oils and Their Chemopreventive Potential

Chemoprevention is a method of controlling cancer with which the development of the illness can be completely avoided, slowed down, or reversed by one or more organic or inorganic substances. Annona might offer an indispensable choice besides chemotherapy

and radiotherapy, especially for terminally ill patients, as the Annona genus contains secondary metabolites, including phytochemicals, antioxidants, essential oils, FAs, minerals, and vitamins, in nearly every component of Annona plants [40,83]. The structure of bioactive substances affects their ability to treat or prevent cancers. The efficiency of cytotoxic activity is determined by the high number of hydroxyl groups supported by the hydroxyl position flanking the γ-lactone ring and the stereo-chemical configuration of the ring [84,85]. Researchers have recently focused on the anticancer effects of Annona seeds, including ASSO, AMSO, and ARSO, and unique chemical compounds extracted from Annona have shown anticancer activities, which allows for further improvements to the available treatment methods, and this research needs to continue to allow for the development of more efficient but less expensive treatments against cancer [86–88].

4.1. Fatty Acids in Annona Seed Oils

FAs are usually found as components of many complex lipid molecules and can be identified as SFAs or UFAs based on the hydrogen atom bonding to the carbon atoms in the molecule. UFAs can be either MUFAs (mono-unsaturated fatty acids) or PUFAs [66]. In terms of composition, unlike animal oils that are made up mainly of SFAs, ASOs contain varying proportions of SFAs and UFAs tied in their TAG (triacylglyceride) molecules, and the percentage of UFAs is higher than that of SFAs (i.e., FAs esterified to a glycerol moiety). Additionally, this makes ASO an interesting source of two PUFAs; linoleic and linolenic acids, which are termed EFAs (essential fatty acids) because humans must obtain them from their diets. TAG is the principal means of storing FAs in biological systems and is considered cytotoxic [89].

The oil and fat available in Annona seeds consist of different FA compositions and lipid profiles. By utilizing the GC/MS method to examine the methyl esters of the seed oil's fatty oil, it is possible to ascertain the chemical composition of the oil [90]. In order to be an oil that is nontoxic for humans, the concentration of linoleic acid and oleic acid should not be more than 12% and 1%, respectively, of that of FA methyl esters, according to European guidelines. Despite being toxic, ASO has large levels of UFAs, particularly oleic and linoleic acids. After detoxification, ASO can also be consumed because it contains a lot of UFAs [91]. Consumed oils have a significant impact on human physiology, including lipid metabolism, chronic illness prevention, and general well-being [92–96]. ASO can be widely used to cure cancer because it includes oleic acid, linoleic acid, stearic acid, palmitic acid, and other UFAs [97].

The physio-chemical properties, such as melting point, solid fat index, saponification value, cloud point, flash point, iodine value, color, viscosity, density, specific heat, and the heat of fusion, etc., of oils are largely dependent on the nature of their constituent FA and TAG compositions. Nonetheless, the FA and TAG compositions of different oils from diverse sources mostly determine their qualitative features and applications, and some of them can become source materials for functional lipids [73,98]. In this context, the FA type, the degree of saturation or desaturation, the method of delivery to cancer cells or hosts, and the tumor/cell type must be considered when evaluating the effects of FAs on tumor cell lines [99]. In the literature, the cytotoxic effects of FAs have been individually evaluated in different tumor cell lines with differing results [100–104]. For example, ASSO has been shown to suppress H22 solid tumor development and show selective cytotoxic activity against HepG2 cell lines, which might be attributed to the presence of UFAs and acetogenins [105].

According to the criteria adopted by the American National Cancer Institute and some cytotoxic screening assays, a crude extract oil showing an IC50 value < 30 $\mu g \cdot mL^{-1}$ in tumor cell lines is considered promising for anticancer drug development [106]. Since ASO has a high content of UFAs, a well-known antineoplastic activity, and different cytotoxic effects have been reported for some species of Annona, its cytotoxic effects against tumor and non-tumor cell lines should be further studied [107,108].

4.2. Phytochemicals in Annona Seed Oils

Plant species rich in phytochemicals are believed to reduce disease risk and have therapeutic characteristics, thus having potential medicinal value [91]. Phytochemicals are secondary metabolic compounds, namely acetogenins, alkaloids, phenolic compounds, essential oils, flavonoids, terpenoids, cyclopeptides, carotenoids, amino acids, etc. (Figure 3). Some phytochemicals, such as acetogenins, have shown neurotoxicity in in vitro and in vivo studies. More research is needed to quantify the number, of neurotoxic compounds and to determine the level of human exposure. Metabolic studies are also necessary to determine whether digestive processes decrease or increase the bioactivity and/or neurotoxicity of the active compounds. These studies have been extended to ASOs used in medicinal treatments [109].

Due to their capacity to scavenge potentially damaging free radicals, it has been discovered that the pharmacological effects of ASOs, including anticancer properties, are connected to the availability and content of phytochemicals and are influenced by the structure of these bioactive compounds. Annona has attracted the interest of individuals interested in the utilization of natural compounds that play a crucial role in the food and pharmaceutical industries [84,85]. Due to Annona's alleged ethno-medical applications against tumors and cancer, extensive anticancer research has been carried out on these plants [110]. Some studies stated that ASO showed high antioxidant activities and phenolic contents and thus may have therapeutic uses [111,112].

The most prevalent bioactive molecules in the Anonaceace family are Anonaceous acetogenins, a special class of long-chain FA derivatives produced via the polyketide pathway. More than 120 acetogenins have been discovered in earlier phytochemical studies on Annona's leaves, stems, bark, seeds, pulp, and fruit peel [113]. Solamin, annoreticulin-9-one, annomonicin, squamone, and rolliniastatin are the principal five annonaceous acetogenins with cytotoxic properties [87]. The mechanism of acetogenin's cytotoxic action is the inhibition of mitochondrial complex I [114] and the inhibition of ubiquinone-linked NADH oxidase in the plasma membranes of cancerous cells, causing apoptosis [115]. A broad class of naturally occurring secondary metabolites is called alkaloids, and they are derived from amino acids or the transamination process [116]. Isolated and reported alkaloids include anomurine, anomuricine, isoquinoleic alkaloids, anonaine, and isolaureline [117]. Since the majority of phenolic compounds are water-soluble and the conventional medicinal extract is an aqueous infusion, they are regarded as the most significant phytochemicals [118].

The important bioactive constituents of ARSO are alkaloids, tannins, flavonoids, cardiac glycosides, phenols, terpenoids, steroids, and saponins [62]. The phytochemical concentrations ranged from 0.16 mg/100 g to 16.15 mg/100 g, with phenol found to be significantly prevalent, whilst tannins, alkaloids, and flavonoids were found to be moderately prevalent, and terpenoids and steroids had the lowest prevalence [119–121]. In general, flavonoids have the potential to significantly reduce the risk of disease through a variety of physiological processes, including cytotoxic and antioxidant actions [7]. Acetogenins have been identified from ARSOs, and some of these substances have demonstrated strong cytotoxic action against four human cancer cell lines (Table 4). The biological activity of annonacin was investigated after further purification, and it was discovered that this substance killed cells in several cancer cell lines. The biological effects of squamocin were also examined, and this research demonstrated that squamocin is a cytotoxic component for almost all cancer cell lines [122–124].

According to preliminary phytochemical analyses, the biological actions of ASSO are primarily brought on by phenolic chemicals such as alkaloids, peptides, amino acids, sterols, tannins, flavonoids, polysaccharides, and tocopherols, which are known to have strong anticancer activities, and they can be used to treat or prevent a variety of illnesses, including cancer [12,125–128]. ASSO has demonstrated substantial antitumor activity in vitro and in vivo against human hepatoma cells, suggesting the potential for the extract to be developed as a novel anti-liver cancer medication [129,130]. An earlier investigation

into the pharmacology of ASSO revealed that it has specific cytotoxic effects on the HepG2 cell line [131].

Table 4. Reported cytotoxic activities of acetogenins present in ASOs.

Seed Oil	Acetogenins	Reported Cytotoxic Activities
Annona reticulata seed oil *	bullatacin cis-/trans-isomurisolenin cis-/trans-bullatacinone annoreticulin annoreticulin-9-one cis-/trans-murisolinone squamocin annonacin squamocin	- strong cytotoxic action against human cancer cell lines, including breast cancer (CCM2), mouth epidermal cancer (Hep.G2 and Hep.2, 3, 15), and liver cancer (Hep.G2 and Hep.2, 3, 15) - cytotoxic for other cancer cell lines, including the HeLa and HeLa S3 cervical cancer cell lines, the SKOV3 and PA-1 ovarian cancer cell lines, the BCC-1 skin cancer cell line, and the MCF-7 breast cancer cell line - apoptosis was induced as a result of encouraging the production of the Bax protein and raising caspase 3 activity - kills cells in several cancer cell lines, including T24 bladder cancer cells - blocks the c-test - cytotoxic component for almost all cancer cell lines
Annona squamosa seed oil **	12, 15-cis-squamostatin-A bullatacin squadiolin A, squadiolin B, squadfosacin B	- significant anticancer capabilities against the cancer cells A-549, Hela, MCF-7, and HepG2, particularly for Hep G2 and MCF-7 - taken orally to inhibit the growth of hepatic cancer cell (H22) lines in mice - significant anticancer activity in animals carrying H22 xenografts; its inhibitory rate was 53.54% against the growth of H22 cell lines - significantly damages MDA-MB-231 - significantly cytotoxic to the breast cancer cells MDA-MB-231 - extremely hazardous to human Hep G2 and 3B hepatoma cells as well as MCF-7 breast cancer cells, and it demonstrates cytotoxicity against HepG2, Hep 3B, and the MCF-7 cell line
Annona muricata Seed oil ***	muricins muricatetrocin A muricatetrocin B longifolicin corossolin corossolone annotacin A and B	- cytotoxic effects on leukemia cells CCRF-CEM - significantly harms the human hepatoma cell lines Hep G2 and 2,2,15 in in vitro experiments - in vitro tests using the human hepatoma cell lines Hep G2 and Hep 2.2.15 revealed strong antiproliferative effects

* Chang et al. [122]; Yuan et al. [123]; Yuan et al. [124]; ** Chen et al. [69]; Chen et al. [129]; Liaw et al. [132]; Yang et al. [133]; *** Kuete et al. [134]; Chang et al. [135].

The total acetogenin content in ASSO was 41.00 mg/g, and it exhibited remarkable cytotoxic activities against human tumor cell lines in a study and helped treat cancers of the liver, cervix, pancreas, etc. [69,129]. The study showed that various acetogenin types exhibit various inhibitory effects against various cancer cells (Table 4), and they have been shown to be the major bioactive compounds that possess strong antitumor/anticancer activity [112]. Using high-performance liquid chromatography (HPLC), two significant acetogenins have been identified in ASSO: 12, 15-cis-squamostatin-A (47.98 mg/g) and bullatacin (256.18 mg/g). Other constituents with antitumor activities include annosquacin A, B, and C, annosquatin A and B, squamostanin A, B, and D, squamostolide, and uvarigrandin A. Although it has been established that the fundamental mechanism is the stimulation of apoptosis, ASSO shows selectivity for certain cancer cells. Free radical production is also considered to be a key mechanism for the anticancer action of seed oils [129,133].

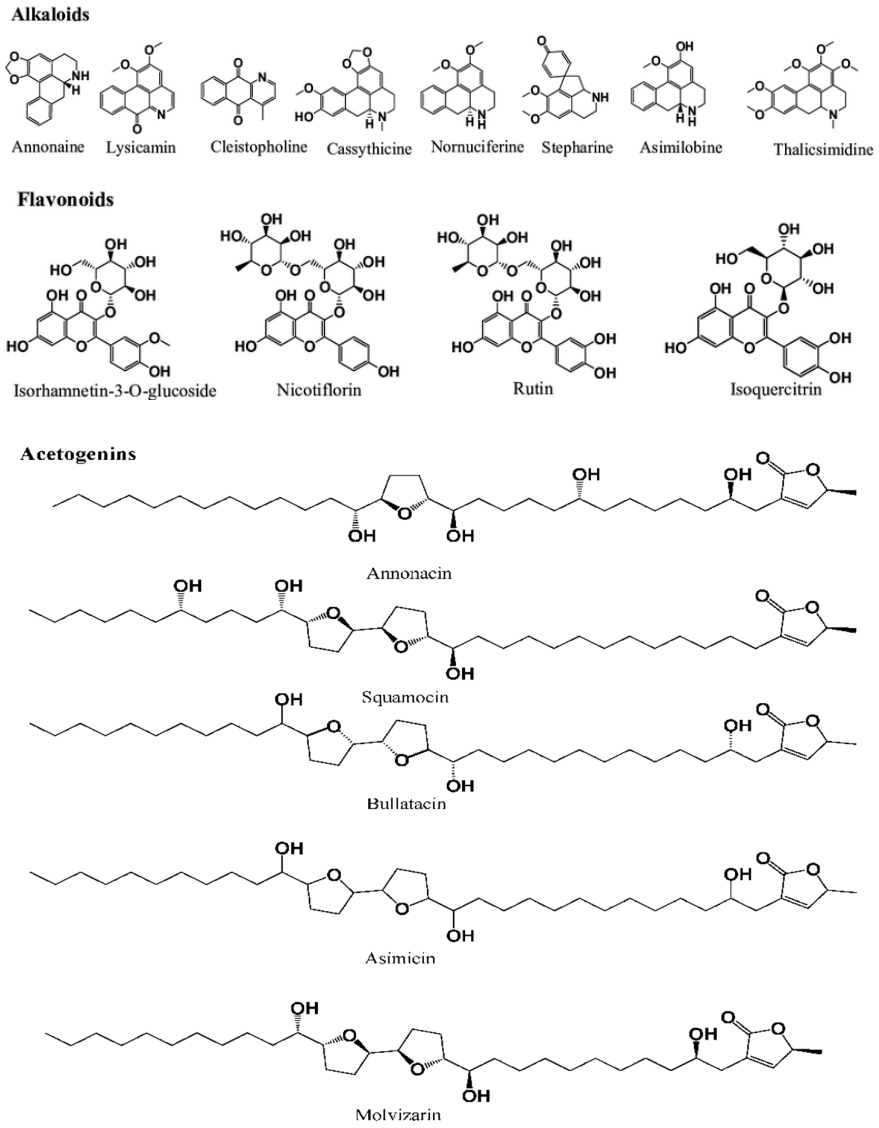

Figure 3. Structures of a few phytochemicals present in ASSO, ARSO, and AMSO [136].

Cancer cells are frequently treated with *A. muricata*, and the entire plant has a promising future as a chemotherapeutic treatment for cancer, according to research. AMSO contains about thirty-seven phenolic compounds, such as acetogenins, alkaloids, phenolic compounds, etc. [137]. In addition to the vitamins and carotenes found in seeds, there have also been shown to be 37 volatile chemicals and 18 essential oils. It improves the capacity of non-cancerous cells in the body. Higher levels of flavonoids are present, which are crucial for reducing cancer cell migration and cellular proliferation, both of which cause a response to reactive oxygen species (ROS) [138]. AMSO-containing acetogenins play a crucial role in preventing cancers (Table 4). Soursop seeds are low in toxins such as tannins, phytates, and cyanides and are high in oil and vitamins [53]. Accordingly, ASOs have huge potential to be used in chemoprevention, which needs to be researched further.

4.3. Antioxidant Activity of Annona Seed Oils

Natural antioxidants include nitrogen compounds such as alkaloids, amino acids, peptides, and amines and derivatives of chlorophyll, carotenoids, and ascorbic acid, as well as phenolic compounds such as flavonoids, phenolic acids, and tannins [139]. Food antioxidants have a significant impact on maintaining good health and are directly linked to the prevention of degenerative diseases like cancer, cardiovascular disease, and neurological disorders [140]. Free radicals such as peroxide, hydroperoxide, or lipid peroxyl, which

are harmful to the body, causing cancer, aging, and cellular damage, are scavenged by antioxidants and prevent the oxidative processes that cause degenerative illnesses [141]. Omega-3 (n-3) UFAs have been linked to cancer prevention [142]. Reactive oxygen species (ROS), also known as oxygen free radicals, play a dual role in biological systems, where both beneficial and detrimental effects are possible [143].

Different antioxidant screening methods were used to examine Annona's capacity to scavenge free radicals, and the findings showed that ASO has significant antioxidants. Additional research may result in the development of powerful antioxidant agents from ASOs [110,144]. Antioxidant-based chemoprevention has been proposed to have a promising future in the provision of significant fundamental advantages to public health. Many scientists and medical professionals are now considering this as a crucial tactic for preventing, postponing, or even stopping the development of cancer [145]. Although numerous research studies have found a correlation between plant phenolic content and antioxidant capacity, it was noted that data about the antioxidant potential of ASO are rare to find [146]. To develop products, cosmetics, nutraceuticals, and biopharmaceuticals to combat cancer and to add to the database of highly significant medicinal plants, further investigation is needed to identify the bioactive compounds responsible for antioxidant activity [147].

Using a DPPH assay, a study found that ASSO has antioxidant activity, with an IC50 value of 7.88 g/mL [130]. In a different investigation, the antioxidant activity of oral-administered ASSO was evaluated in rats (150–210 g) with alcohol-induced liver damage. Superoxide dismutase, glutathione, and catalase levels were shown to be significantly raised following treatment with the ethanolic seed extract [77]. As a result, ASSO therapy results in the restoration of normal antioxidant enzymes. Through oral administration, ASSO reduced the development of H22 tumor cells in mice by a maximum inhibitory rate of 53.54% [69].

In addition to the six previously reported cytotoxic acetogenins annoreticuin, annoreticuin-9-one, cis-/trans-bullatacinone, bullatacin, cis-/trans-murisolinone, and squamocin, cis-/trans-isomurisolenin was also discovered [146,148]. There have also been reports of spathenelol, muurolene, copaene, and eudesmol, among other terpenes. Cyclohexapeptide glabrin A was recovered from a methanol extract of ARSO, and novel cyclooctapeptides were discovered by analyzing the sequence and three-dimensional structure of cycloreticulins A and B. N-fatty acyl tryptamines were also obtained [148,149]. AMSOs contain a considerable amount of antioxidants, and the antioxidant activity of soursop seed oil was 77.34% (dry basis) [150].

Mother nature has provided us with many naturally occurring medicinal plants, yet we often use them without realizing their therapeutic value [151]. Several medicinal plants have been examined scientifically, and it has been found that their secondary metabolites and bioactive chemicals have the potential to have an anticancer impact. The best example of this is the *Annona* species. The chosen *A. squamosa*, *A. muricata*, and *A. reticulata* have also grown in favor as a result of more modern research being conducted on the bioactivities and health benefits of various plant parts, such as the seeds, bark, leaves, fruits, etc. Although the seeds of the fruit are usually waste and the fruit itself is edible, literature reviews have reported that ASO primarily consists of fatty acids, phytochemicals, and antioxidants like polyketides, annonaceous acetogenins (neurotoxins), cyclopeptides, carbohydrates, proteins, lipids, oleic acid, and linoleic acid. The phytochemical composition and molecular basis of the bioactivities of Annona seeds have been the subject of a few studies. The demand for innovative treatments is growing as a result of the wide variety of cancer types and their primary causes. A novel cancer medication that can target and prevent apoptosis in cancer cells is the subject of intense research efforts today. Accordingly, it has been noted that plants of the same species collected from various areas have varying levels of secondary metabolites, indicating that the synthesis of a plant's bioactive components may also vary, impacting how effective it is against cancer cells [16,152].

In conventional medicines, Annona is regarded as an ideal source of pharmacologically active compounds. Several prior investigations on the biological functions of the various

Annona spp. components have been conducted [153,154]. Annona seed oil contains phytochemicals, antioxidants, and fatty acids found in ARSO, AMSO, and ASSO, which are employed for the treatment of cancer. In vitro and in vivo studies that show their usefulness in chemoprevention have been explored, as have anticancer agents. Fatty acid-derived lipids serve as the building blocks for cell membrane formation in addition to being crucial for hormone and signal transmission [155]. Due to their rapid proliferation and division, tumor cells require a lot of FAs. FAs make up a large portion of ASO. Tumor cells will undoubtedly absorb more ASO. Additionally, ASO primarily enters cells through passive transport [156].

5. Conclusions

ASOs were found to be effective in key bioactivities, including antioxidant activity and antitumor/anticancer activity, and based on in vivo and in vitro investigations, secondary metabolites of ASO cause anticancer and other immune system-associated effects. This review outlined the many pharmacological effects, particularly the aforementioned species' anticancer properties. To undertake thorough investigations and gain a better grasp of Annona's anticancer potential, more studies will eventually need to be conducted. The bioactive substances that contribute to its bioactivities have also not been correctly identified or qualitatively and quantitatively studied as chemical markers for standardization and quality control purposes, and their mechanisms of action need to be adequately established. Therefore, there is a ton of room for further research into the phytochemical and pharmacological properties of ASOs to support their legitimate place in evidence-based chemopreventative medications. Hence, to isolate and identify the active metabolites that contribute to their robust anti-inflammatory and anticancer actions, future research on ASOs should concentrate on broad phytochemical investigations. Before being submitted to clinical trials to determine their safest concentration, their active metabolites should also be subjected to more mechanistic studies, in vivo and in vitro investigations, and toxicity tests. Further improvements to available treatment methods need to continue to allow for the development of more efficient but less expensive treatments against cancer.

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