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Biological Activities of Plants from Genus *Annona*

Norma Francenia Santos-Sánchez,
Raúl Salas-Coronado, Beatriz Hernández-Carlos,
Aleyda Pérez-Herrera and
Dora Jhanina Rodríguez-Fernández

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Abstract

Species of the genus *Annona* (Annonaceae) are distributed in the tropical and subtropical regions of the world and are characterized by their highly valued exotic fruit. The commercial species are *A. muricata*, *A. crassiflora*, *A. squamosa*, *A. cherimola*, and *A. reticulata*. In addition, different parts of the tree, including leaf, bark, and roots, are used in traditional medicine to treat conditions such as diabetes, hypercholesterolemia, hypertension, cancer, and gastrointestinal diseases. Phytochemical studies are helping to determine the biological properties of extracts and characterize bioactive principles from extracts of genus *Annona*. The main chemical compounds isolated from genus *Annona* are phenols, acetogenins, alkaloids, and cyclopeptides. All these compounds have antioxidant properties and generally are associated with other biological properties. The aim of this chapter is to carry out an analysis of the properties related to combating oxidative stress of the five most important species of the genus *Annona*, as well as the relationship these properties have with the bioactive principles present in these plants.

Keywords: genus *Annona*, phenols, acetogenins, antioxidant, antitumor, antidiabetic

1. Introduction

Bioactive compounds are extra nutritional constituents present in small amounts in higher plants. They reinforce the immune system, combat oxidative stress, and reduce the risk of a number of diseases, especially cancer, diabetes, and cardiovascular diseases [1]. Traditional medicine has developed diverse treatments based on the use of plant extracts with well-known results worldwide. Based on these results, *in vitro* and *in vivo* studies, mainly with mice and rats, have

been carried out to validate the effects described. Studies have been done to identify and classify the chemical compounds responsible for the biological properties. *Annona* have been used traditionally for medicinal and nutritional purposes. Pinto et al. published a monograph that addresses the main medicinal uses of plants of the genus *Annona* in detail in one of its chapters [2]. Additionally, Moghadamtousi et al. conducted a review of the traditional uses of *A. muricata* [3].



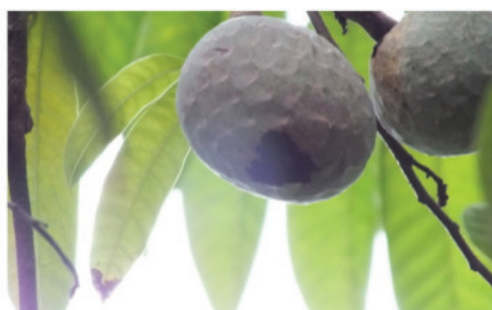
Annona muricata

Annona crassiflora



Annona squamosa

Annona cherimola



Annona reticulata

Figure 1. Photographs of the five *Annona* species reviewed in this chapter. The images of *A. muricata*, *A. squamosa*, *A. cherimola* and *A. reticulata* were obtained from <https://www.inaturalist.org/taxa>, while the image of *A. crassiflora* was obtained from <http://tropical.theferns.info>.

A. muricata is one of the best known and most studied species of the genus *Annona*. However, there are other species of this genus that produce edible fruit, such as *A. squamosa*, *A. crassiflora*, *A. cherimola*, *A. reticulata*, etc., which are also highly valued and used in traditional medicine. *Annona* fruit contains a considerable quantity of phenolic compounds and other bioactive compounds [4, 5]. Many of these compounds are antioxidants that can help with the prevention and treatment of diseases like cancer, atherosclerosis, diabetes mellitus 2, etc. [6–8].

Another group of compounds are the acetogenins, which are a chemical group representative of the genus *Annona*. These compounds are polyketides that are characterized by linear chains of 32–34 carbons with hydroxyl, ketones, epoxides, tetrahydrofurans, and tetrahydropyrans groups. Acetogenins comprise more than 450 compounds isolated mainly from species of the genus *Annona*. The properties of acetogenins are closely associated with their antiproliferative activity on cancer cell lines. This activity is related to the reduction of ATP levels and the induction of apoptosis. In addition, other biological properties have been demonstrated, including antineoplastic, antiparasitic, cytotoxic, immunosuppressive, neurotoxic, etc. [9]. Alkaloids and cyclopeptides with potent antiulcer and anticancer activity are also present in *Annona* extracts.

The objective of this chapter is to carry out a critical review of the biological properties of extracts of the five most important *Annona* species (*A. muricata*, *A. crassiflora*, *A. squamosa*, *A. cherimola*, and *A. reticulata*) **Figure 1**, as well as associating the biological properties with the bioactive principles present in the extracts.

2. Genus *Annona*

The review is organized by species, and the principal studies for every species discussed are described. The methods of evaluation of antioxidant and other activities are briefly mentioned. The reports demonstrate the diversity of the chemical structures present in *Annona* species; among them, phenols, acetogenins, and alkaloids are found. This chapter describes some of these compounds and their relation to corresponding biological properties.

2.1. *Annona muricata*

A. muricata L. is known as soursop, graviola, paw-paw, and sirsak and is native to the warmer tropical areas of America. It has also been found in some tropical and subtropical regions, including India, Malaysia, and Nigeria. *A. muricata* is a perennial, terrestrial, upright tree that reaches 8 m in height and has an open canopy, with roundish, large, bright, dark green leaves. The edible fruit of the tree is large, heart-shaped, and green, with a diameter between 15 and 20 cm [10]. *A. muricata* has antihypertensive [11], antidiabetic [12–14], antimalarial [15], antiviral [16], anthelmintic [17], anticonvulsant [18], antibacterial [19], antioxidant [20], and anticancer [21–25] properties. Florence et al. evaluated the antidiabetic activity of aqueous extracts at concentrations of 100 and 200 mg of extract·(bw)^{−1} and found that the polar extract of *A. muricata* reduced blood glucose level, body weight, food and water intake, lipid profile, and oxidative stress to near normal. These results can be attributed to antioxidant and protective effects of pancreatic β -cells of *A. muricata* extracts [13]. In the same study, Florence et al.

administered, for 28 consecutive days, an aqueous extract from *A. muricata* at doses of 100 and 200 mg·kg⁻¹ to rats with diabetes induced by streptozotocin (STZ) [13]. Streptozotocin, in addition to inducing diabetes, promotes an increase in triglycerides, total cholesterol, low-density lipoprotein, atherogenic index, and a decrease in high-density lipoprotein. After 4 weeks of treatment with the aqueous extract, a reduction in triglycerides, total cholesterol, low-density lipoprotein, and high-density lipoprotein concentrations was observed. In addition, a decrease in the hepatic levels of aspartate aminotransferase and alanine transferase, as well as malonaldehyde in liver and kidney, and an increase in the levels of superoxide dismutase and catalase in liver, kidney, and aorta were seen. *A. muricata* contains 212 different bioactive compounds including phenolic compounds [26], which have been shown to have an antidiabetic and anti-inflammatory effect. Damayanti et al. evaluated, through a computational study, the potency of *A. muricata* as FOXO1 inhibitor for diabetes mellitus treatment [14]. The results of this study showed that the main components responsible for FOXO1 inhibition were anonaine (1), xylopine (2), isolaureline (3), kaempferol 3-O-rutinoside (4), rutin (5), and muricatocin A (6), **Figure 2**. This inhibition ability is possible because the compounds are capable of strongly and spontaneously binding with the active site of FOXO1.

Pieme et al. evaluated *in vitro* the antiproliferative activity and apoptosis induction of extracts coming from three different parts of *A. muricata* at concentrations in the range of 1–100 µg·mL⁻¹ against human promyelocytic leukemia (HL-60) cells [22]. The authors concluded that *A. muricata* has the potential as a chemotherapeutic and cytostatic agent against HL-60 cells because it induced loss of cell viability, morphology changes, loss of membrane mitochondrial potential, and G0/G1 phase cell arrest **Figure 3**. Yang et al. carried out a study that demonstrated synergistic

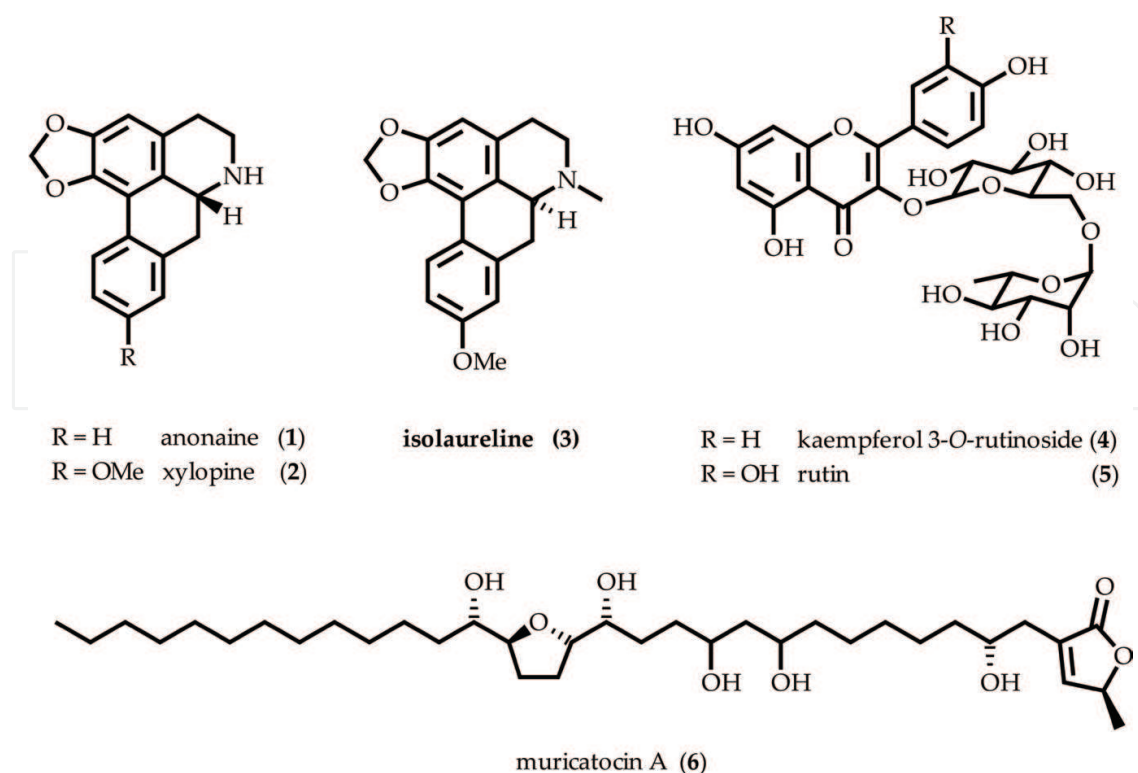


Figure 2. Molecules with FOXO1 inhibition activity isolated from *Annona muricata* [14].

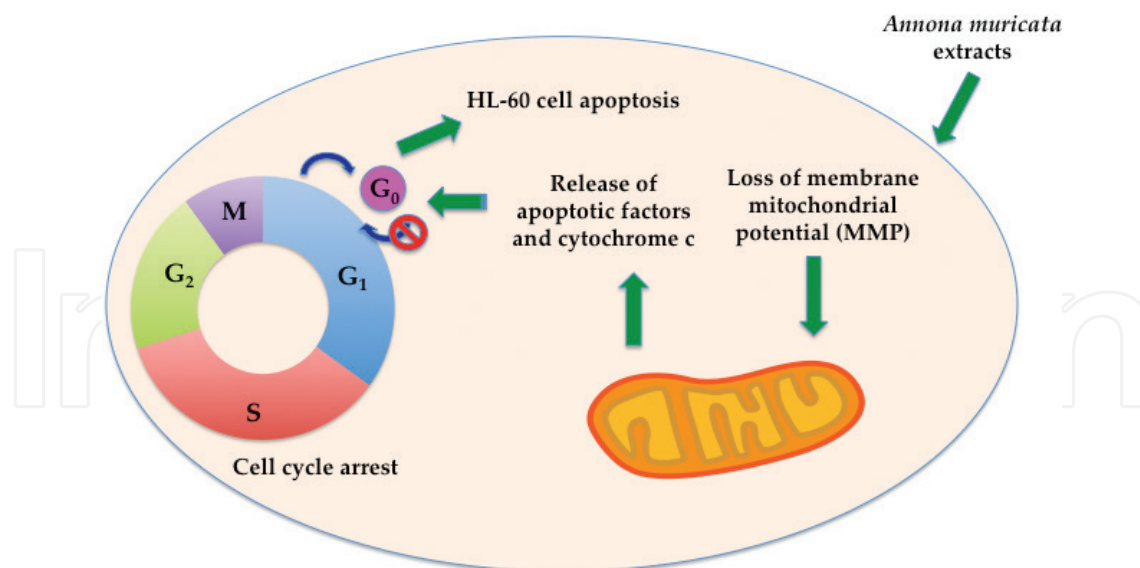


Figure 3. Schematic representation of mechanism for *Annona muricata* extracts-induced HL-60 cell apoptosis. G₀ = quiescence, G₁ = Gap 1, S = DNA replication/synthesis, G₂ = Gap 2, M = mitosis.

interactions between flavonoids and acetogenins of leaf extracts from *A. muricata* against prostate cancer [27]. This study was conducted with mice exposed to androgen-independent prostate cancer (PC-3) cells that were fed with dichloromethane (CH₂Cl₂), acetic acid (AcOH), ethyl acetate (EtOAc), ethanol (EtOH), or methanol (MeOH) extracts from leaves of *A. muricata* at doses of 100 mg of extract·(kg of body weight (bw))⁻¹. The acetogenins that were supplied as part of an extract from *A. muricata* leaves were more effective than acetogenin-enriched fractions, which were toxic and in some cases led to the death of the mice. Generally, the extracts used are polar, containing significant quantities of antioxidant compounds [19].

2.2. *Annona crassiflora*

Annona crassiflora is known as araticum, araticum-do-cerrado, ariticum, articum, marolo, bruto, cabeça-de-negro, pinha-do-cerrado, and pasmada [29]. *A. crassiflora* is a perennial, terrestrial, upright tree that reaches 6–8 m in height and has oval, coriaceous leaves. *Annona crassiflora* has antioxidant [28], antimicrobial [29, 30], antidiabetic [31], hepatoprotective [32], antiobesity [33], and anticancer [34] activities. Débora and Neuza carried out a study of the lipid extract of *A. crassiflora* Mart. seeds, identifying and quantifying fatty acids, phytosterols and tocopherols, as well as evaluating the antioxidant activity expressed as radical DPPH• scavenging. The results of this study showed that the lipid fraction of *A. crassiflora* Mart. seed contains a relevant quantity of tocopherols (expressed as α-, β-, γ-, and δ-tocopherol) and phytosterols (campesterol, stigmasterol, and β-sitosterol) with a content of 683.59 and 138.90 mg·kg⁻¹, respectively. They also showed that the antioxidant activity was significantly influenced by the phytosterols and the fatty acids composition of the sample [28]. Cavalcante et al. evaluated the antimicrobial activity of EtOH extracts from *A. crassiflora* root wood and root bark against *Candida albicans* [29]. The minimum inhibitory concentration (MIC) of extract used in this study was 2000 µg·mL⁻¹. The authors suggest that the responsible compound for antimicrobial activity is goniodonin, an acetogenin [29]. Another study related to the antimicrobial activity of *A. crassiflora* was made

by Silva et al. [30]. They evaluated the antibacterial activity of ethanol aqueous extracts of fruit rind, stem, seed, pulp, and leaf from *A. crassiflora* against oxacillin-resistant *Staphylococcus aureus*. The stem extract showed a better selectivity index against oxacillin-resistant *Staphylococcus aureus*. The authors reported that the EtOH aqueous extract from *A. crassiflora* contains tannins, a group of phenolic compounds. Justino et al. evaluated the antidiabetic activity expressed as α -amylase, α -glucosidase, and glycation inhibitory activity of extracts rich in antioxidant compounds from *A. crassiflora* fruit peel [31]. The results of this study showed that fractions of EtOAc and *n*-butanol from 98% EtOH aqueous extract have a high antioxidant activity and α -amylase and α -glucosidase inhibitory activities. The spectrometric analysis revealed the presence of caffeoyl-glucopyranoside

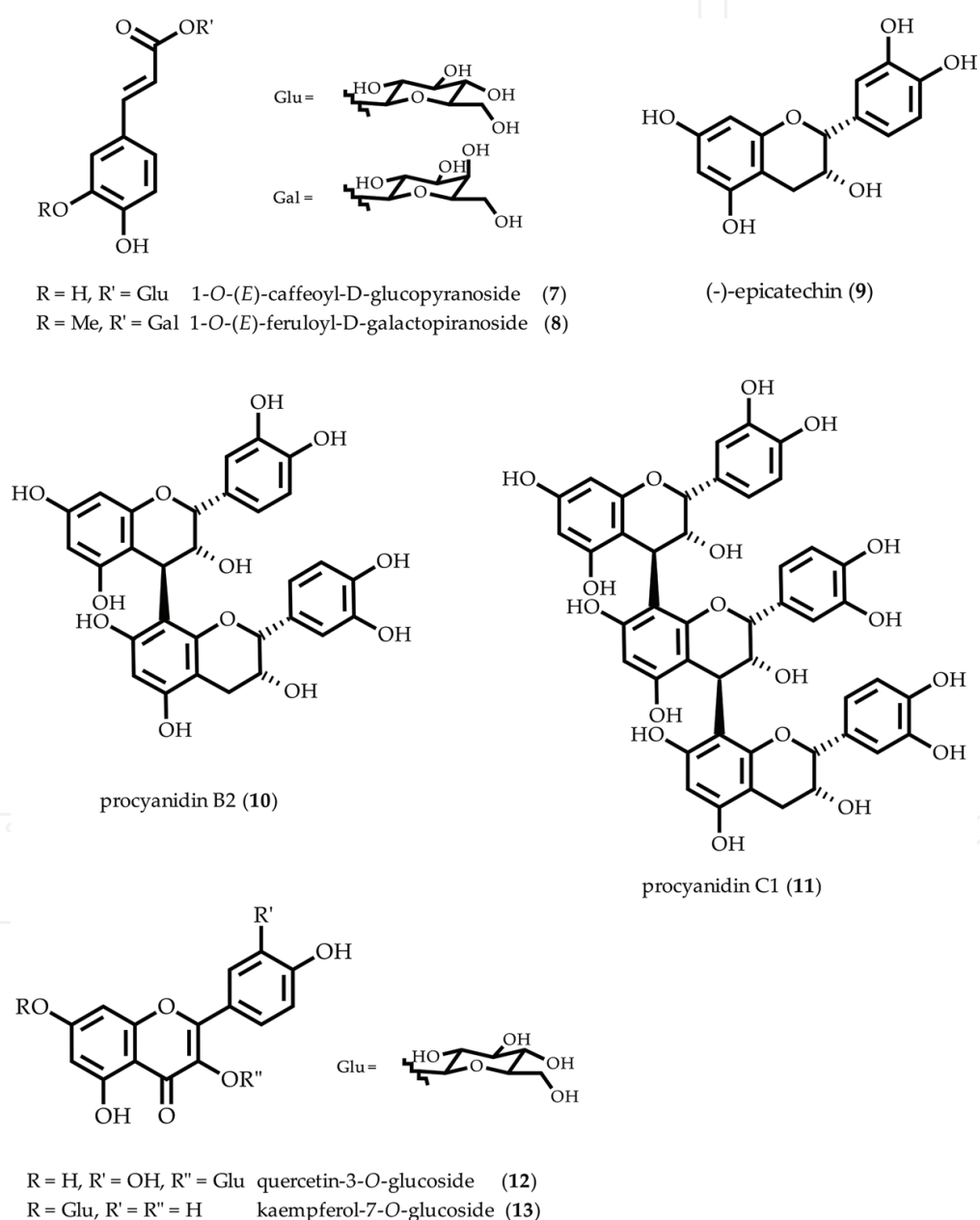


Figure 4. Main bioactive compounds of *Annona crassiflora* fruit peel with antioxidant capacity and α -amylase, α -glucosidase, and glycation inhibitory activities [31].

(7), feruloyl-galactopyranoside (8), (–)-epicatechin (9), and procyanidin B2 (10) in both fractions. In addition, in the EtOAc fraction, the study identified procyanidin C1 (11) and the flavonoids quercetin-3-*O*-glucoside (12), kaempferol-7-*O*-glucoside (13), **Figure 4**, and rutin (5), **Figure 2**. Roesler evaluated the effect of EtOH extracts from *A. crassiflora* fruit on the hepatic antioxidant enzymes using Wistar rats with CCl₄-induced liver damage [32]. The results showed that ethanol extracts of *A. crassiflora* fruit could enhance or maintain the hepatic activity of antioxidant enzymes, such as catalase, glutathione peroxidase, and glutathione reductase. This effect can be attributed to ascorbic acid (14), xanthoxylin (15), caffeic acid (16), ferulic acid (17), caffeoyltartaric acid (18), **Figure 5**, and flavonoid 5, **Figure 2**. All these compounds are potent antioxidants present in *A. crassiflora* fruit.

2.3. *Annona squamosa*

Annona squamosa is known as sweetsop, sugar apple, custard apple, ata, saramuya, and Aztec. The *A. squamosa* tree is deciduous and much smaller than the *A. muricata*, reaching a maximum height of 6.0 m, with abundant lateral branches. Shirwaikar et al. evaluated the effects of the consumption of aqueous extracts of *A. squamosa* leaves in diabetic rats for 12 days [35]. The doses used were 250 and 500 mg·kg^{–1} (both doses without toxicity), and plasma glucose levels, serum insulin levels, liver glycogen levels, level of reactive substances to thiobarbituric acid (TBARS), and pancreatic and blood lipid levels (cholesterol and triglycerides) were measured with fasting. A significant reduction in plasma glucose was found 30 min after the oral glucose tolerance test. In addition, plasma glucose levels and serum insulin levels decreased significantly with the two doses administered. The aqueous extracts of *A. squamosa* contain a large quantity of mucilages, which are analogous to gums (soluble fraction of the fiber), which have been shown to have a powerful role in the treatment of hyperglycemia and hyperlipidemia [36]. Insulin is an important inhibitor of lipolysis in adipose tissue and the release of fatty acids into the bloodstream; when there is a deficiency of this hormone, dyslipidemia can be induced [37, 38]. In this same study, rats that did not receive *A. squamosa* extract had twice as high triglyceride and cholesterol levels. In addition, a significant increase in hepatic glycogen levels was observed in diabetic rats treated with the aqueous extract, probably due to a reactivation of the glycogen synthase system. The effects of diabetes include the affecta-

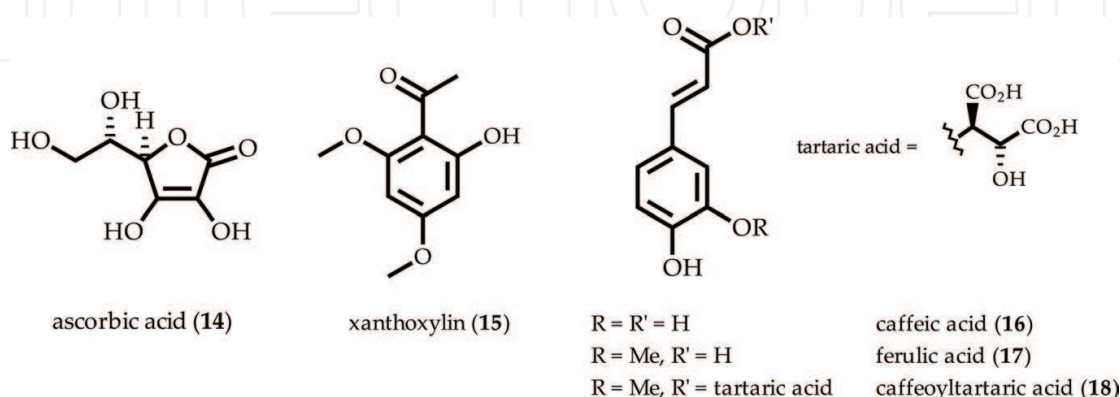


Figure 5. Antioxidants from *Annona crassiflora* [32].

tion of glycogen synthesis in the liver and skeletal muscle [39]. The diabetic rats treated with the aqueous extract of *A. squamosa* increased in weight, probably due to a protective effect in the control of energy expenditure of muscle. Shirwaikar et al. [35] also found that *A. squamosa* extract showed antioxidant activity by decreasing TBARS levels in the pancreas. Numerous studies indicate that oxidative stress plays an important role in the pathogenesis of diabetes and its complications. Both insulin resistance and beta cell dysfunction, two central events in the pathogenesis of diabetes mellitus 2, have been linked to a redox imbalance [40]. Thus, it has been found that *A. squamosa* extracts have significant amounts of phenols and flavonoids, which may be involved in the reduction of oxidative stress associated with diabetes. Finally, the antidiabetic activity was independent of doses administered at concentrations of 250 and 500 mg·kg⁻¹ of extract. Gupta et al. [41] evaluated the effect of ethanolic extracts of *A. squamosa* leaves in different doses (200, 300, 350, and 400 mg·kg⁻¹) on glucose tolerance in diabetic rats (induced with streptozotocin). It was found that the hypoglycemic effect occurred 1 h after glucose loading and was maintained up to 3 h. The EtOH extracts of *A. squamosa* were administered to diabetic rats in a single dose of 350 mg·kg⁻¹ for 15 days. The levels of total cholesterol, low-density lipoproteins, very low-density lipoproteins, and triglycerides, which after treatment with the extract were high, decreased significantly 15 days after treatment. In addition, an increase of 30.3% in high-density lipoproteins was found. El-Chaghaby et al. evaluated the effect of different polar solvent extracts on the antioxidant and antibacterial activities of *A. squamosa* leaves [42]. The antioxidant activity was evaluated using the phosphomolybdenum method, reducing power assay and hydrogen peroxide-scavenging assay. Antibacterial activity was evaluated using six test bacterial species (*Bacillus subtilis*, *Escherichia coli*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus faecalis*). The results showed moderate antibacterial activity with respect to a standard antibacterial agent and this activity correlates positively with the phenolic contents. These compounds were found to be the major contributor to the antioxidant and antibacterial activity of polar extracts from *A. squamosa* leaves. In a different study, Rahman et al. evaluated extracts and four compounds from *A. squamosa* seeds for antimicrobial activity [43]. Three of these compounds were acetogenins [annotemoyin-1 (19), annotemoyin-2 (20), and squamocin (21)], **Figure 6**. The antimicrobial activity was evaluated against 10 bacteria species [five gram (+) and five gram (-)]

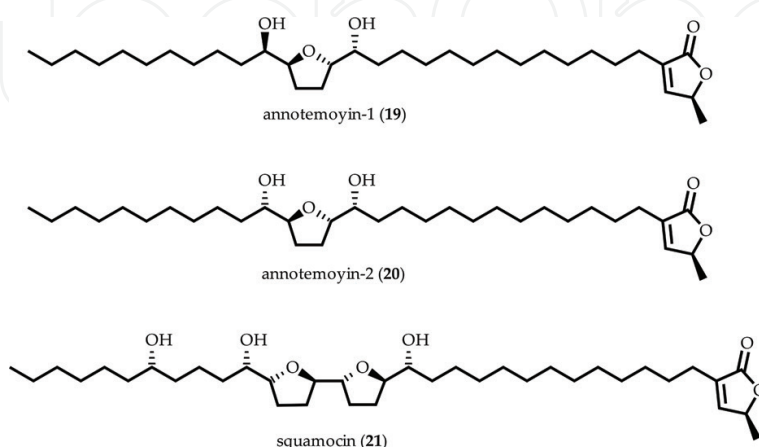


Figure 6. Acetogenins isolated from the seeds of *Annona squamosa* with antimicrobial and cytotoxic activities [43].

and four fungi. The results showed that acetogenins have antibacterial activities against all test microorganisms at MIC in the range of 60–130 $\mu\text{g}\cdot\text{mL}^{-1}$.

Yadav et al. evaluated antiulcer activity in rats of extracts and 11 compounds isolated from *A. squamosa* twigs [44]. The models used in this study were cold-restraint-induced gastric ulcer, aspirin-induced gastric ulcer, and pyloric ligation-induced ulcer; they also used histamine-induced duodenal ulcer in guinea pigs and *in vitro* assay of H^+ , K^+ -ATPase activity. Extracts of *A. squamosa* twigs at concentrations of 25, 50, and 100 $\text{mg}\cdot\text{kg}^{-1}$ were used. The results showed that ethanol extracts of *A. squamosa* twigs inhibit *in vitro* H^+ , K^+ -ATPase (proton pump) activity and simultaneously strengthen the mucosal defense mechanism **Figure 7**. The compounds (+)-*O*-methylnorpavine (22), *N*-methylnorpavine (23), and isocorydine (24) were the active components of the extract, **Figure 8**. Zahari et al. found that alkaloid 24 has antioxidant activity with DPPH assay, metal-chelating activity assay, and ferric-reducing antioxidant power assay (FRAP) [45].

2.4. *Annona cherimola*

Annona cherimola is a tropical tree native to Peru and Ecuador. The word cherimoya comes from the Quechua name “chirimuya,” which means “cold seeds” [46]. The tree is small, upright, and/or somewhat spreading, deciduous with a maximum height of 7.5 m. Its trunk frequently divides at the ground level into several trunks [47]. *A. cherimola* has been cultivated since the Incan Empire, dating back to 1200 BC. Albuquerque et al. evaluated the antioxidant activity of extracts from pulp, peel, and seeds of *A. cherimola* fruit [48]. The results showed a significant

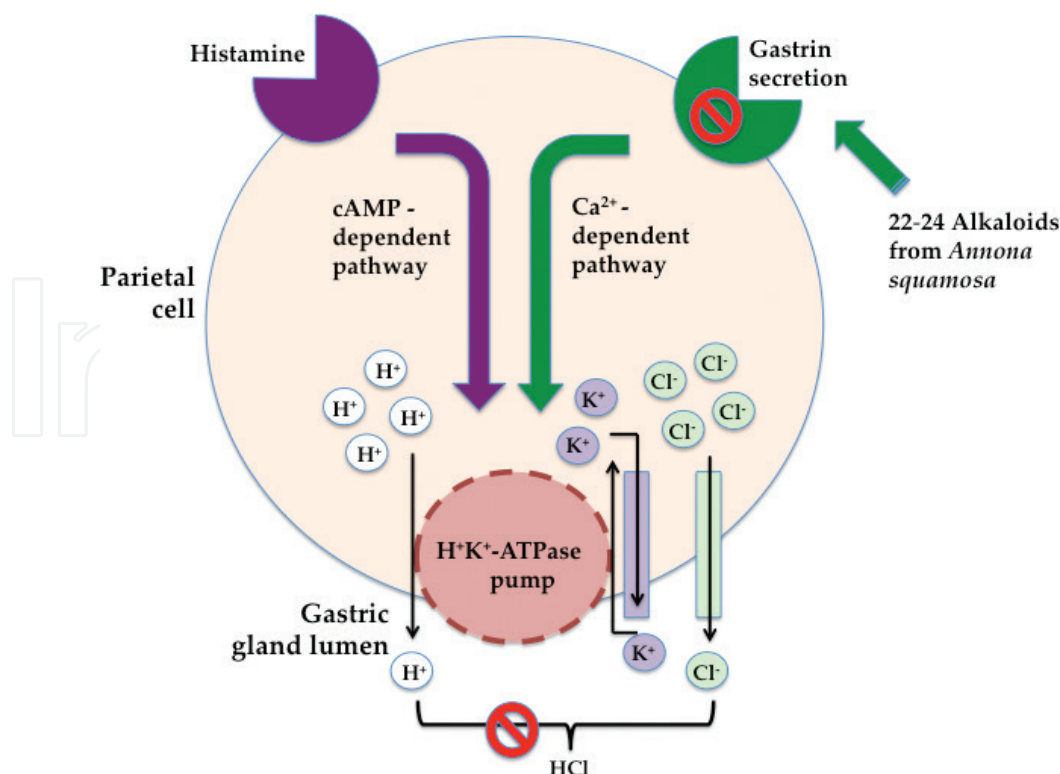


Figure 7. Inhibition of H^+K^+ -ATPase activity by alkaloids 22-24 from EtOH extracts of *A. squamosa* twigs.

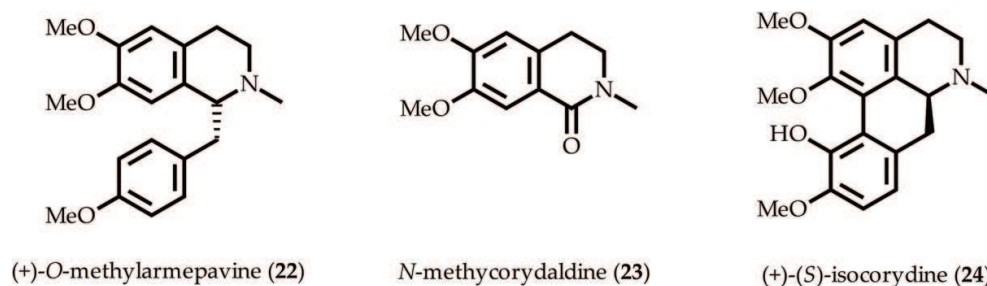


Figure 8. Alkaloids from *Annona squamosa* with antiulcer effect *in vivo* [44].

antioxidant activity of *A. cherimola* fruit, mainly in the peel. These results are similar to those reported by Loizzo et al. who examined the antioxidant properties of *A. cherimola* pulp and peel and found that the peel extract showed the greater capacity for free radical-scavenging DPPH $\cdot$ and ABTS $\cdot^+$ and good antioxidant activity through FRAP assay, β -carotene bleaching assay, and Fe $^{2+}$ chelating assay [49]. The peel extract showed the highest content of phenols and flavonoids. Gupta-Elera et al. evaluated antioxidant properties of *A. cherimola* fruit *in vitro* using the oxygen radical absorbance capacity (ORAC) assay and simulating conditions of cells under oxidative stress. The results showed that *A. cherimola* peel, pulp, and juice have antioxidant activity [50]. The juice showed the highest antioxidant activity, while the pulp exhibited the lowest. The results also indicate that pre-exposure to oxidative stress may contribute to an increased antioxidant uptake in both Raji (Burkitt's lymphoma) and HT-29 (colon cancer) cell lines. In the two cell lines, cell lysate antioxidant capacity was significantly higher when cells were exposed to oxidative stress. This is an indication that oxidative stress contributed to the uptake of antioxidants as a response mechanism. Barreca et al. evaluated antioxidant and cytoprotective properties of extracts from the pulp of *A. cherimola* fruit [51]. The extracts from *A. cherimola* pulp had powerful antioxidant activity expressed as scavenging activity toward DPPH $\cdot$, ABTS $\cdot^+$, O $_2^{\cdot-}$ radical, and ferric-reducing antioxidant power (FRAP) assay, while the ethanol extract showed the highest activity against lipid peroxidation induced by *tert*-butyl hydroperoxide. García-Salas et al. carried out an exhaustive study of identification and quantification of phenolic compounds in *A. cherimola* fruit [52]. The method used for identification and quantification was HPLC-DAD-ESI-QTOF-MS. The main results indicate the presence of 21 phenolic and organic acid compounds in the edible portion of *A. cherimola* fruit, 37 in the peel and 22 in the seeds. The *A. cherimola* seeds contain acetogenins, *cis*-annonacin (25), and (2,4)-*cis*- and *trans*-isoannonacins (26 and 27, respectively), **Figure 9**. These acetogenins showed cytotoxicity against the human tumor lines A-549 (lung carcinoma), MCF-7 (breast carcinoma), HT-29 (colon adenocarcinoma), A498 (renal carcinoma), PC-3 (prostate adenocarcinoma), and MIA PaCa-2 (pancreas carcinoma), with a remarkable selectivity to this last line with a power of 1000 times higher than adriamycin [53]. Adriamycin is a commercial anticancer (antineoplastic or cytotoxic) chemotherapy drug. This compound is classified as an anthracycline antibiotic. Earlier, Kim et al. isolated and evaluated the anticancer activity of annomolin and annocherimolin. Annomolin has anticancer activity against the PC-3 line and annocherimolin against the MCF-7 and HT-29 lines [54]. Cyclopeptides with anticancer activity have also been isolated from the seeds of *A. cherimola*. For example, cherimolacyclopeptide C (28), cherimolacyclopeptide E (29), and cherimolacyclopeptide F (30) showed significant cytotoxicity against tumor cells KB (nasopharyngeal carcinoma), **Figure 10** [55, 56].

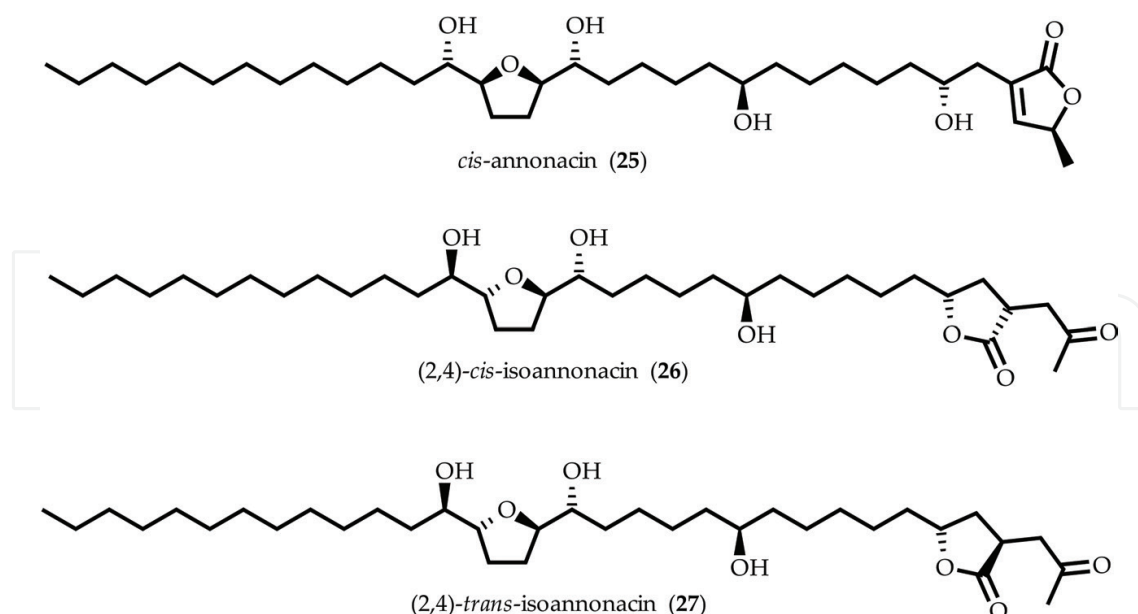


Figure 9. Acetogenins with cytotoxicity activity from seeds of *Annona cherimola* [52].

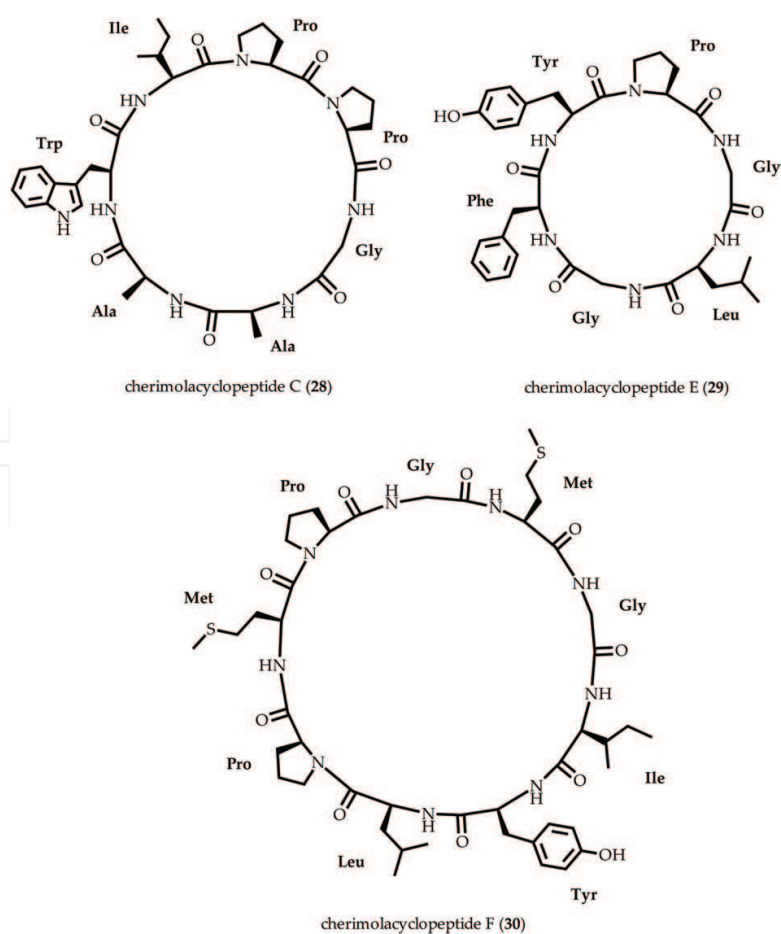


Figure 10. Cyclopeptides with anticancer activity isolated from the seeds of *A. cherimola* [54].

Arun et al. carried out a review related to the pharmacological potential of *A. cherimola* and found antidiabetic activity of leaf extract in streptozotocin (STZ)-induced hyperglycemia in rats [57]. The extract effect was evaluated by measuring fasting plasma glucose levels, serum insulin levels, serum lipid profiles, and body weight in normal rats. In addition, the measurement of liver glycogen levels and pancreatic lipid peroxidation levels was considered for diabetic rats [58]. A significant reduction in blood glucose level and a loss of body weight in diabetic rats were observed. Calzada et al. recently evaluated antihyperglycemic activity of *A. cherimola* leaves on alloxan-induced diabetic rats. The effect of ethanol extract at concentrations of $300 \text{ mg}\cdot\text{kg}^{-1}$ was measured through the blood glucose level [59]. A computational molecular docking was also done to show the interaction of flavonoid **5**, **Figure 2**, with enzyme α -glucosidase. Calzada et al. confirm that rutin (**5**) is the main compound responsible for antihyperglycemic activity of *A. cherimola* leaves. Before this study, Fale et al. found that **5** is the main compound in decoctions of *A. cherimola* leaves, responsible for inhibiting the HMG-CoA reductase activity and decreasing the cholesterol uptake in intestinal cells [60]. HMG-CoA reductase is the dependent enzyme of NADH, which controls the mevalonate pathway rate, which produces cholesterol.

2.5. *Annona reticulata*

Annona reticulata is a small deciduous tree that is grown in diverse parts of the world, including southern and eastern Asia, central and southern America, Australia, and western Africa. It grows up to 10 m in height. The leaves are narrow, lanceolate, alternating, and oblong, measuring approximately 10–20 cm long and 2–5 cm wide with conspicuous veins and a bad odor [61]. Extracts from different parts of *A. reticulata* have shown antioxidant and antimicrobial [62], antihyperglycemic [63, 64], and anticancer [65, 66] activities. Jamkhande et al. (2014) evaluated antioxidant and antimicrobial activity of root extract from *Annona reticulata*. The antioxidant activity was evaluated by DPPH free radical-scavenging assay and antibacterial and antifungal activities by agar cup method and poison plate method, respectively. The results of this study showed that methanol extracts of *A. reticulata* roots have significant antioxidant activity and a wide spectrum antibacterial and antifungal efficacy [61]. Gینگine et al. (2016) evaluated the anticancer activity of methanol extract from *Annona reticulata* leaves [64]. This activity was investigated for anticancer potential using sulforhodamine B (SRB) cytotoxicity assay against colon cancer (HCT15), human lung cancer (Hop65), and human hepatoma (HEPG2) cell lines. The extract exhibited a moderate anticancer effect against all the cell lines. Suresh et al. (2011) evaluated the anticancer activity of ethanol extract from *Annona reticulata* roots against melanoma cells in mice and *in vitro* activity on MDA-MB-435 human melanoma cells by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay [65]. The ethanol extract exhibited significant *in vitro* and *in vivo* inhibitory activities against melanoma tumor cells. In both studies, the anticancer activity is attributed to the presence of acetogenins in the extracts used to perform the evaluations. Rahman et al. evaluated antihyperglycemic activity of methanol extract from *A. reticulata* leaves in Swiss albino mice [63]. The extracts were administered at doses of 50, 100, 200, and $400 \text{ mg}\cdot\text{kg}^{-1}$. The results showed lowered blood sugar in mice, and the authors suggest that the responsible compounds are acetogenins. Acetogenins have been reported from the plant seeds [66]. These compounds, including squamone (**31**), solamin (**32**), annomonicin (**33**), and rolliniastatin 2 (**34**), have also been isolated from the leaves (**Figure 11**) [67]. Santos Lima et al.

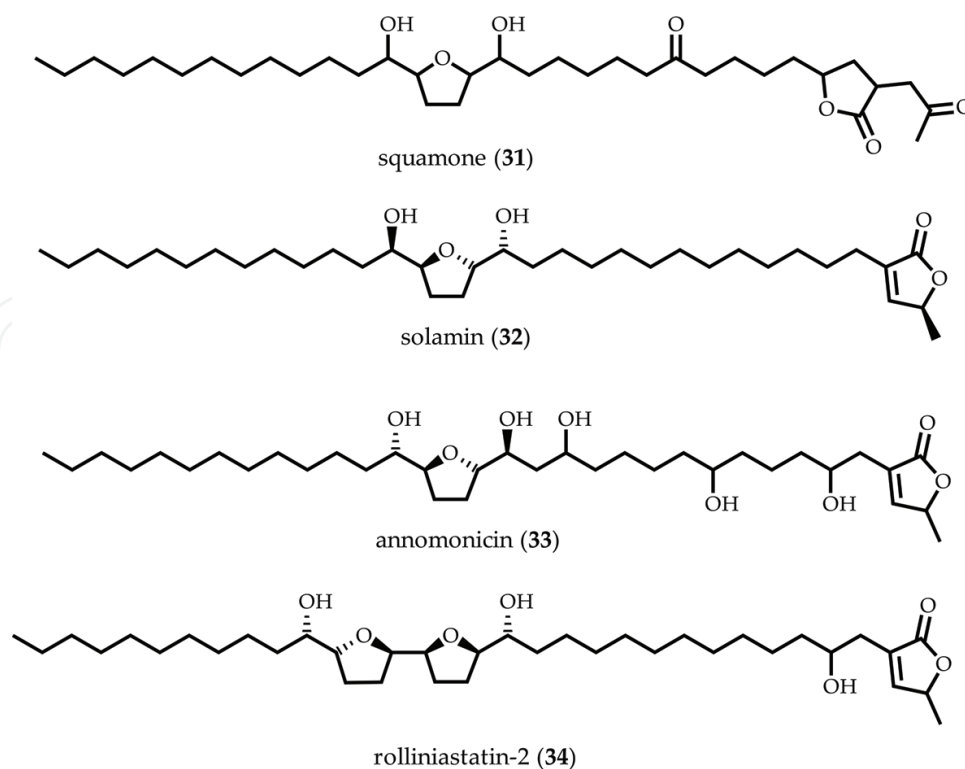


Figure 11. Acetogenins isolated from *A. reticulata* leaves [67].

evaluated the antioxidant activity of acetogenins and found that they have strong DPPH radical-scavenging activity, like that of ascorbic acid [68].

3. Conclusion

After analyzing the five most studied species of genus *Annona*, it can be concluded that they have great potential for the treatment of diseases associated with oxidative stress, including diabetes, hyperglycemia, cancer, and gastric ulcers, among others, because they are rich in antioxidant compounds. The most studied species of this genus are *A. muricata* and *A. cherimola*. The stems, trunks, and leaves of the trees are the most frequently studied and used in traditional medicine. Undoubtedly, the most representative bioactive compounds of the genus *Annona* are the acetogenins because they are abundant, mainly in the seeds of the fruit. There are several studies that show the anticancer properties of the genus. In addition, the phenolic compounds found in this genus are capable of inducing antioxidant properties in extracts. It is also possible to find alkaloids and cyclopeptides with properties similar to acetogenins in the species of this genus.

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Conflict of interest

The authors have no conflict of interest to declare and are responsible for the content and writing of the manuscript.

Ethical approval

This chapter does not contain any studies with human participants or animals performed by any of the authors.

Author details

Norma Francenia Santos-Sánchez¹, Raúl Salas-Coronado^{1*}, Beatriz Hernández-Carlos¹, Aleyda Pérez-Herrera² and Dora Jhanina Rodríguez-Fernández¹

*Address all correspondence to: rsalascoronado@hotmail.com

¹ Institute of Agroindustry, Universidad Tecnológica de la Mixteca, Oaxaca, Mexico

² CIIDIR-Oaxaca, Instituto Politécnico Nacional Hornos, Santa Cruz Xoxocotlán, Oaxaca, Mexico

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