ABSTRACT

Plants have been significantly used in traditional medicine by a variety of societies since antiquity, and knowledge of their safety, efficacy, and quality value can be developed through further research. The genus *Annona*, consisting of 119 species, has been extensively researched and proven to have a diverse range of pharmacological activities such as antioxidant, antiulcer, antiinflammatory, antidiarrheal, and antiparasitic. This is because the *Annona* plants possess a great number of phytochemicals found in almost every part of the plant, which can be isolated to be developed into herbal medicine. Phytochemicals are classified into several classes, such as Annonaceous acetogenin, alkaloids, flavonoids, and essential oils. This article was created by collecting 124 research articles which discuss phytochemical compounds from 20 species and the pharmacological activity from 13 species.

1. Introduction

Natural products, specifically those derived from plants, have helped mankind in many aspects of life, particularly medicine. Plants possess extremely high potential to be developed as medicine. Nevertheless, usage of natural medicines should also consider safety, efficacy, and quality. Therefore, research on medicinal plants from compound isolation to pharmacological activity testing is carried out to improve treatment standards.

The genus of *Annona* is part of the Annonaceae family and includes approximately 119 species. Most species of *Annona* grow in tropical America, except for *Annona senegalensis*, which grows in tropical Africa. Members of the genus grow as deciduous shrubs or small trees, whose height ranges from 5 to 11 meters. The stem is hairy when young, with color ranging from rusty to grayish (Bhardwaj et al., 2019). The *Annona* plant’s uses in traditional medicine have been widely known, such as the antiinflammatory effect of plants *Annona muricata*, *Annona reticula*, and *Annona salmellani*; plants *Annona cherimola*, *Annona squamosa*, and *A. reticula* for antiparasitic uses; the anti-inflammatory effect from using *A. salmellani* and *Annona vepretorum*; along with other uses (Egydio-Brandão et al., 2017).

Based on the great potential of these plants as drug candidates and the large body of available research on the *Annona* plant, a literature review is necessary in order to summarize part of the results. This review is intended to provide the public with knowledge of the potential and benefits of *Annona* plants. Therefore, a review of the phytochemical compounds and pharmacological activities of the *Annona* genus was created by collecting and analyzing past research articles. The inclusion criteria are the sources come from over the last 25 years, has a minimum H-Index of 17, and has quartile score 1 until 3. The exclusion criteria are the sources come from over the last 25 years, has a minimum H-Index is less than 17, and has quartile score of 4.

2. Phytochemistry of *Annona*

A wide range of phytochemical compounds from nearly every part of the *Annona* plants have been successfully discovered, isolated, and characterized by variety of methods. Each compound is classified into several classes according its’ characteristics such as Annonaceous acetogenins, alkaloids, flavonoids, megastigmanes, steroids, and essential oils (Table 1).

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<td>Thalicsimidine</td>
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*A. salzmannii*  
Bark  
Anonaine  
Asimilobine  
Cleistopholine  
Lirioidenine  
Reticuline  

Leaves  
Bicyclogermacrene, (E)-caryophyllene, and α-copaen 

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<th>Part</th>
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<th>Class</th>
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<td>(+)-catechin</td>
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*A. senegalensis*  
Aerial parts  
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Leaves  
(-)-roemerine  

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<td>γ-cadinene</td>
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Seed  
Annogalene, Annosenegalnine  

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<td>Oxoaporphines</td>
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*A. squamosa*  
Bark  
2,4-cis-Mosinone A  
2,4-trans-Mosinone A  
Annoreticum-9-one  
Mosin B  
Mosin C  

Leaves  
(-) Anonaine  
O-methylarmepavine  
β-Caryophyllene, β-Cedrene  
Bicyclogermacrene, (E)-Caryophyllene, Germacrene D  
Quercetin-3-O-glucoside  

Pulp Fruit  
α-pinene, Limonene, Sabinene  

Seed  
Annosquamins A, Annosquamins B, Annosquamins C  

Stem  
11 ent-kauranes  
10-nor-ent-kaurane-4α, 16β, 17-triol  
16α, 17-dihydroxy-ent-kauran-19-al  
16α, 17-dihydroxy-ent-kauran-19-oic acid  
16α-hydro-19-al-ent-kauran-17-oic acid  
16β, 17-dihydroxy-ent-kauran-19-al  
16β, 17-dihydroxy-ent-kauran-19-oic acid  
16β-hydro-ent-kauran-17, 19-dioic acid  
16β-hydroxy-17-acetoxy-ent-kauran-19-oic acid  
17-hydroxy-16β-ent-kauran-19 oic acid  
4α-hydroxy-19-nor-ent-kauran-17-oic acid  
ent-kaur-16-en-19-oic acid  

*A. sylvestris*  
Leaves  
Hinesol; z-Caryophyllene; β-Maaliene; γ-Gurjunene; Silphiperforol-5-en-3-ol; Ledol; Cubecol-1-epi; Murola-3, 5-diene.  

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<td>Meira et al. (2014)</td>
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<td>α-phellandrene, Bicyclogermacrene, Spathulenol</td>
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phytochemical compounds: antinociceptive (Carballo et al., 2010), anti-acetylcholinesterase (Lee et al., 2015), anticonvulsant (Eva Gonzalez-Trujano et al., 2013), antidepressant (Martinez-Vazquez et al., 2012), antibacterial (Takahashi et al., 2006), antifungal (Navarro Garcia et al., 2003), anticaner (Ajaiyeoba et al., 2005), antidiabetic (Panda and Kar, 2007), anti-diarrhea (Afroz et al., 2020), antiulcer (Castillo-Juarez et al., 2009), anti-inflammatory (Rocha et al., 2016), antimalarial (Ajaiyeoba et al., 2005), dengue vector control activity (de Omena et al., 2007), antioxidant (Essama et al., 2015), and antileishmanial (Lima et al., 2012) (Table 2).

3.1. Antinociceptive, anti-acetylcholinesterase, anticonvulsant, and antidepressant activities

Antinociceptive compounds have analgesic effect resulting in reduction of pain. Ethanol crude extract from *Annona diversifolia* leaves had a comparable antinociceptive response (ED$_{50}$ = 15.35 mg/kg) to tramadol, the reference drug, (ED$_{50}$ = 12.42 mg/kg) when evaluated with the writhing test in mice (Carballo et al., 2010). Fifteen alkaloids derived from *A. glabra* leaves through fractionation using centrifugal partition chromatography (CPC) possess anti-acetylcholinesterase activity. The compounds (−)-anolobine and (−)-roemeroline indicated moderate inhibitory activity against cell acetylcholinesterase with IC$_{50}$ values of 22.4 μM and 26.3 μM (Lee et al., 2015).

*A. senegalensis* crystals obtained from *A. senegalensis* root bark fraction indicated anticonvulsant activity. *A. senegalensis* crystals were characterized as kaur-16-ene-19-oi acid then orally administrated to mice with (PTZ)-induced seizures, providing LD$_{50}$ value of 3800 mg/kg (Okeye et al., 2013). Supporting its use in traditional medicine, the aerial parts of *A. cherimola* had therapeutic potency as an antidepressant (Martinez-Vazquez et al., 2012).

### Table 2. Pharmacological activities of plants from the *Annona* genus.

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<th>Pharmacological Activity</th>
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<td>Lee et al. (2015)</td>
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<td>Leaves</td>
<td>Eva Gonzalez-Trujano et al. (2006); Cano-Europa et al. (2010)</td>
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<tr>
<td>Anticancer</td>
<td><em>A. sylvatica</em></td>
<td>Leaves</td>
<td>Formagio et al. (2013)</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td><em>A. squamosa</em></td>
<td>Leaves</td>
<td>Panda and Kar (2007)</td>
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<tr>
<td>Antidiabetic</td>
<td><em>A. cherimola</em></td>
<td>Leaves</td>
<td>Calzada et al. (2017)</td>
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<tr>
<td>Antidiabetic</td>
<td><em>A. muricata</em></td>
<td>Leaves</td>
<td>Adeyemi et al. (2009)</td>
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</table>
3.2. Antibacterial and antifungal activity

Acetogenins in *A. cherimola* leaves had antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* with inhibitory diameter of 14 mm and 11 mm, respectively. *A. amboiy* also had antibacterial activity with diameter of 10 mm and 9 mm, respectively (Takahashi et al., 2006). Another *Annona* plant, *A. squamosa*, has high potency antibacterial activity, especially its seed compounds. The methanol extract, chloroform extract, and petroleum ether extract of *A. squamosa* could inhibit *Escherichia coli*, *Pseudomonas aeruginosa*, *S. aureus*, *Klebsiella pneumonia*, and *B. subtilis* (Aher et al., 2012). The water-methanol extract worked against *S. aureus* with Minimum Inhibitory Concentrations (MIC) of 50 mg/mL and Minimum Bactericidal Concentrations (MBC) of 100 mg/mL (Mohamad et al., 2017).

Besides antibacterial activity, *Annona* plants also have antifungal activity. Ethanol extract from the leaves of *A. crassiflora* was active against all microorganisms and indicated antifungal activity based on the MIC values of 57 inhibited strains of *Candida albicans* (Silva et al., 2008). The sesquiterpenes of essential oils from the leaves of *A. salzmannii* show MIC values of 1 mg/mL for *C. albicans* and 0.5 mg/mL for *Candida tropicalis* (Costa et al., 2011a).

3.3. Anticancer activity

Cancer is a common cause of death worldwide. Nowadays, several methods performed to cure cancer are surgical treatment, radiotherapy, and chemotherapy. Therapy is the main method to cure this disease, but it is still not accessible for many people. Anticancer herbal drugs have been developed, especially from *Annona* plants (Wang et al., 2014).

An aporphine alkaloid from *A. senegalensis* leaf extract, (−)-roemerine, was found to increase the cytotoxic response mediated by vinblastine with multidrug-resistant KB-V1 cells. Evaluation of the cytotoxic potential was conducted with cultured P-388 cell and KB-V1 treated with vinblastine (1 μg/mL). The results indicated ED$_{50}$ value of > 5 μg/mL of P-388 cell and ED$_{50}$ value of 0.6 μg/mL of KB-V1 cell with vinblastine (1 μg/mL) (You et al., 1995). In other plants, anticancer activity was shown by cytotoxicity test with IC$_{50}$ value of 27.2 μg/mL for *A. pickelii* leaf essential oil, 89.7 μg/mL for *A. salzmannii* leaf essential oil (Costa et al., 2013) and 1.36 mg/mL for *A. muricata* leaf (Asare et al., 2015).

3.4. Antidiabetic activity

Diabetes or hyperglycemia is a disease characterized by increasing in sugar blood levels due to certain factors. The development of herbal remedies from *Annona* plant has been conducted abundantly. In a preclinical study using hyperglycemia-induced rats, methanol extract of *A. muricata* leaf could decrease blood glucose concentration from 26.64 mmol/L until 4.22 mmol/L in the test group (Adeyemi et al., 2009). The leaves of *A. cherimola* also have high antidiabetic potential, could decrease blood glucose concentration from 331.5 mg/dL to 149.2 mg/dL. Routine administration as α-glucosidase inhibitor could increase antidiabetic activity (Calzada et al., 2017).  

3.5. Antidiarrhea and antitumor activity

*A. muricata* has been traditionally used for a long period of time. Testing of the *A. muricata* fruit methanol fraction showed 58.38% inhibition of diarrhea at a dose of 400 mg/kg body weight in Swiss albino mice (Afroz et al., 2020). As another example, the stem-bark extract of *A. senegalensis* was tested using the intestinal transit time of mice method. The extract at the dose of 10 mg/kg significantly decreased intestinal transit time at concentrations of 0.2 – 3.2 mg/mL (Suleiman et al., 2008). Therefore, antidiarrhea activity in *A. muricata* and *A. senegalensis* has been scientifically proven.
water extract (Castillo-Juarez et al., 2009). Administration of A. squamosa twig extract using doses of 25, 50, 100 mg/kg body weight on rats with cold-restraint induced ulcer indicated percentage protection of 50%, 87.50%, and 81.20%, respectively, whereas omeprazole (10 mg/kg) as reference drug showed 77.4% (Yadav et al., 2011).

3.6. Anti-inflammatory activity

Inflammation can occur due to development of tissue lesions, which cause pain from edema exerting pressure on nerve endings. The kaempferol 3-O-β-glucoside and kaempferol 3-O-β-diglucoside from A. crassiflora leaves might inhibit the occurrence of edema. Doses of 100 mg/ kg and 300 mg/kg can inhibit the formation of carrageenan-induced edema to about 53% and 47% (Rocha et al., 2016). The essential oil from the leaves of A. sylvaetica at doses of 20 mg/kg and 200 mg/kg showed 19% and 27% inhibition (Formaggio et al., 2013). These results can be used in the development of herbal anti-inflammatory medicine.

3.7. Antimalarial and dengue vector control activity

Malaria is a disease caused by Plasmodium sp. with Anopheles female mosquito as the vector. Plants are rich in compounds with antimalarial effect, such as quinine and artemisinin. The development of antimalarial drugs continues to be conducted, including compounds from Annona plants. The leaves of A. senegalensis were tested on Plasmodium berghei and 91.1% chemosuppression was obtained at dose of 800 mg/kg/day (Ajaiyeoba et al., 2005). Another study tested the bark and leaves of A. squamosa on 3D7 and INDO strains of Plasmodium falciparum. A. squamosa leaves indicated IC_{50} value of 2.1 µg/mL and 3.3 µg/mL on P. falciparum 3D7 and P. falciparum INDO, respectively. Bark of A. squamosa showed IC_{50} value of 30 µg/mL on P. falciparum 3D7 (Kamaraj et al., 2012; Singh et al., 2015).

Besides antimalarial, Annona plants also have Dengue Vector Control Activity. It is evidenced in the two species tested on Aedes aegypti larvae. Stem extracts of A. glabra possess LC_{50} value of 26.9 µg/L against the fourth-instar larvae of A. aegypti (de Mendonca et al., 2005), while seeds of ripe fruits from A. muricata has LC_{50} value of 93.48 µg/mL against the third-instar larvae of A. aegypti (Grzybowski et al., 2013). The potential of Dengue Vector Control of Annona plant is high enough to merit large-scale development as herbal medicine.

3.8. Antioxidant activity

Antioxidants are compounds that prevent or inhibit free radicals. Adverse effects caused by free radicals included decreasing in activity of immune system, cancer, and diabetes. Certain plants have high antioxidant activity, one of them being the Annona plant. Antioxidant activity assay using DPPH method on some parts of A. muricata is indicated by the EC_{50} value of barks amounting to 96 µg/g DPPH, 290 mg/g DPPH for leaves, 116 mg/g DPPH for stems, compared to 157.5 mg/g DPPH for ascorbic acid as reference drug (Essama et al., 2015). On the ORAC method testing of several alkaloid isolated from the bark of A. saltzmanni, asilimoline was found to be the most active with ORAC value of 2.09 relative Trolox equivalents (Costa et al., 2013).

3.9. Antileishmanial activity

Visceral leishmaniasis is an endemic in 88 countries infecting 12 million people. Many phytochemicals from the Annona group were tested against Leishmania. Alkaloids and acetogenins isolated from A. muricata seeds and A. squamosa leaves were tested against promastigote and amastigote forms of Leishmania chagasi. The alkaloids in A. squamosa showed EC_{50} of 23.3 µg/mL against promastigotes and 25.4 µg/mL against amastigotes, while acetogenin show EC_{50} of 25.9-37.6 µg/mL against promastigotes and 13.5-28.7 µg/mL against amastigotes (Vila-Nova et al., 2011). Methanol leaf and seed extracts of A. mucosa presented activity against L. amazonensis with IC_{50} of 28.32 µg/mL and 46.54 µg/mL, respectively. The results of the study displayed that Annona plants possess high antileishmanial potential and deserve further development (Lima et al., 2012).

4. Conclusion

The Annona Genus has several classes of chemical compounds that are found in almost every part of certain Annona plants, such as Annonaceous acetogenins, alkaloids, cyclic peptides, essential oils, flavonoids, megastigmanes, and steroids. Additionally, the Annona plants have many pharmacological effects that have been scientifically proven, such as antinociceptive, anti-acyetylcholinesterase, anticonvulsant, antidepressant, antibacterial, antifungal, anticancer, antidiabetic, antiinflammatory, antilucre, anti-inflammatory, antimalarial, Dengue vector control activity, antioxidant, and antileishmanial. This article was created by collecting 124 research articles discussing phytochemicals from 20 species and the pharmacological activity from 13 species, which can be utilized by the public for knowledge of herbal treatments from Annona plants.

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Conflict of Interest

The authors declare no conflict of interest.

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