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Review Article

Phytochemical and Pharmacological Studies of the genus *Annona:* A Review

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Abstract: Various ancient literature stated plant based chemicals are the most important source of medicine. 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 *Annona* genus consists of 119 species. 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 disease. The pharmacological activities of *Annona* are antioxidant, antiulcer, antidiarrheal, and antiparasitic. A great number of phytochemicals found in almost every part of the plant. Phytochemical studies are helping to determine the biological properties of extracts of genus *Annona*. The main chemical compound isolated from genus *Annona* are phenols, acetogenins, alkaloids, flavonoids, and essential oil. The aim of this review is to analyze the published report based on the medicinal values of different Asian *Annona* species to provide the updated information about the pharmacological as well as the phytochemical properties for the first time.

Keywords: Traditional medicine, Pharmacological activities, Antioxidant, Hypertension, Phytochemical properties.

1. Introduction

The medicinal plants are prosperous in secondary metabolites and essential oils of therapeutic importance. The important compensation claimed for therapeutic uses of medicinal plants in various ailments is their safety also being economical, effective and their easy availability. Because of these compensation the medicinal plants have been widely used by the conventional medical practitioners in their day to day practice. [1] 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.[2] The *Annona* plant's uses in traditional medicine has been widely known, such as the antidiarrheal effect of plants *Annona muricata, Annona reticulata*, and *Annona salzmannii*; plants *Annona cherimola, Annona squamosa,*

and *A. reticulata* for antiparasitic uses; the anti-inflammatory effect from using *A. salzmannii* and *Annona vepretorum*; along with other uses. [3] The plant is also known as Ramphal, Bullock's heart and Custard apple.[4] *Annona* is a semi-evergreen and little deciduous tree as of the plant family Annonaceae.[5] *Annona* is broadly cultivated throughout India, South America and West Indies, also cultivated in Bangladesh and Pakistan. *Annona* is a very apparent plant in ayurvedic technique of medicine for the treatment of different ailments. It is a small tree with glabrous branches which is found in tropical region.[4]

The plant is conventionally used for the cure of epilepsy, dysentery, cardiac problems, worm infestation, constipation, hemorrhage, antibacterial infection, dysuria, fever, and ulcer. It also has antifertility, antitumor and abortifacient properties. Ethanolic extracts of leaves and stem are reported to have an anticancerous activity. The aqueous leaf extract has also reported to improve hyperthyroidism, which is frequently considered as a causal factor of DM. [6] Plants are recognized as aromatic as well as source of medicine. The extracts obtained from various plant parts possess medicinal properties and are used as colouring agent, preservative, sweetening agent and as an additive in many medicinal formulations.[7] Plants restrain abundant amount of secondary metabolites, they are considered to be principal source of therapeutically active compounds. Along with medicinal formulations plants have been successfully utilised for the development of cosmetics and toiletry preparations.[8] Bark contains Kaurenoic acid, phenolic and nonphenolic alkaloids, two crystalline alkaloids–muricine, muricinine, (2, 4-cis and trans)-squamolinone, (2, 4-cis and trans)-9-oxoasimicinone, bullacin B, 4-deoxyannoreticuin-cis-4-deoxyannoreticuin and (2, 4-cis and trans)-squamoxinone, annosquamosin Bas (19-nor-ent-kaurane-4, 16,-17-triol), bullatacin, bullatacinon and squamone, a new bioactive acetogenin Cycloprop (e) azulene, germacrene D, bisabolene, caryophylleneoxide etc.[9] It has Annosquammosin A (16-hydroxy-19-al-ent-kaurane-17-yl-16 -hydro-19-al-ent-kaurane-17-oate), annosquamosin C (16-hydro-17-hydroxy-nor-ent-kauran-4-o1), annosqumosin D (16-acetoxy-17-hydroxy-19-nor-ent-kauran-4-o1), annosquamosin E (16-hydroxy-17-acetoxy-19-nor-ent-kauran-4-formate), annosquamosin F (16-hydroxy-17-acetoxy-18-nor-ent-ent-kauran-4-hydroperoxide), annosquamosin G.[10]

Literature reviews revealed different pharmacological studies including antimicrobial, antidiabetic, antiprotozoal, antioxidant, cytotoxic, anti-proliferative etc. on this species. In Asia, many of the indigenous plants of the genus *Annona* are extensively used in traditional medicine, and various research works were done to investigate their bioactivity and their phytochemical constituent till now. The present article reviews those medicinal values of this genus *Annona* to highlight the significance and the importance of such topical fruits plant species as ethnomedicines.

Whole plant **Bark** **Leaves**

Flower **Root** **Seed**

Figure 1. Morphology of different parts of *Annona*

2. *Annona* Species in Folklore Practice

Folk medicine comprises medical aspects of traditional knowledge that developed over generations within various societies before the era of modern medicine. The World Health Organization (WHO) defines traditional medicine as "the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness". Traditional medicine is contrasted with scientific medicine. In some Asian and African countries, up to 80% of the population relies on traditional medicine for their primary health care needs. When adopted outside its traditional culture, traditional medicine is often considered a form of alternative medicine. Practices known as traditional medicines include traditional European medicine, traditional Chinese medicine, traditional indigenous Mayongia magic and medicine (Assam), traditional indigenous medicine of Assam and rest of NE India, traditional Korean medicine, traditional African medicine, Ayurveda, Siddha medicine, Unani, ancient Iranian Medicine, Iranian (Persian), Islamic medicine, Muti, and Ifá. Scientific disciplines which study traditional medicine include herbalism, ethnomedicine, ethnobotany, and medical anthropology. The WHO notes, however, that "inappropriate use of traditional medicines or practices can have negative or dangerous effects" and that "further research is needed to ascertain the efficacy and safety" of such practices and medicinal plants used by traditional medicine systems. [11] Ultimately, the WHO has implemented a nine-year strategy to "support Member States in developing proactive policies and implementing action plans that will strengthen the role traditional medicine plays in keeping populations healthy."[12]

The study of herbs dates back 5,000 years to the ancient Sumerians, who described well-established medicinal uses for plants. In Ancient Egyptian medicine, the Ebers papyrus from c. 1552 BC records a list of folk remedies and magical medical practices [13]. The Old Testament also mentions herb use and cultivation in regards to Kashrut. Many herbs and minerals used in Ayurveda were described by ancient Indian herbalists such as Charaka and Sushruta during the 1st millennium BC[14]. The first Chinese herbal book was the Shennong Bencao Jing, compiled during the Han Dynasty but dating back to a much earlier date, which was later augmented as the Yaoxing Lun (Treatise on the Nature of Medicinal Herbs) during the Tang Dynasty. Early recognized Greek compilers of existing and current herbal knowledge include Pythagoras and his followers, Hippocrates, Aristotle, Theophrastus, Dioscorides and Galen. Roman sources included Pliny the Elder's Natural History and Celsus's De Medicina[15]. Pedanius Dioscorides drew on and corrected earlier authors for his De Materia Medica, adding much new material; the work was translated into several languages, and Turkish, Arabic and Hebrew names were added to it over the centuries [16]. Latin manuscripts of De Materia Medica were combined with a Latin herbal by Apuleius Platonicus (Herbarium Apuleii Platonici) and were incorporated into the Anglo-Saxon codex Cotton Vitellius C.III. These early Greek and Roman compilations became the backbone of European medical theory and were translated by the Persian Avicenna (Ibn Sīnā, 980–1037), the Persian Rhazes (Rāzi, 865–925) and the Jewish Maimonides.[16] Many countries have practices described as folk medicine which may coexist with formalized, science-based, and institutionalized systems of medical practice represented by conventional medicine[17]. Examples of folk medicine traditions are traditional Chinese medicine, traditional Korean medicine, Arabic indigenous medicine, Uyghur traditional medicine, Japanese Kampō medicine, traditional Aboriginal bush medicine, and Georgian folk medicine, among others.[12]

3. Ethnomedicinal Formulation of *Annona* Species

All portions of the *A. muricata* tree, similar to other *Annona* species, including *A. squamosa* and *A. reticulata* are extensively used as traditional medicines against an array of human ailments and diseases, especially cancer and parasitic infections. The fruit is used as natural medicine for arthritic pain, neuralgia, arthritis, diarrhea, dysentery, fever, malaria, parasites, rheumatism, skin rushes and worms, and it is also eaten to elevate a mother's milk after childbirth. The leaves are employed to treat cystitis, diabetes, headaches and insomnia. Moreover, internal administration of the leaf's

decoction is believed to exhibit anti-rheumatic and neuralgic effects, whereas the cooked leaves are topically used to treat abscesses and rheumatism. The crushed seeds are believed to have anthelmintic activities against external and internal worms and parasites. In tropical Africa, the plant is used as an astringent, insecticide and piscicide agent and to treat coughs, pain and skin diseases. In India, the fruit and flower are employed as remedies against catarrh, while the root-bark and leaves are believed to have antiphlogistic and anthelmintic activities.

In Malaysia, the crushed leaf mixture of *A. muricata* together with *A. squamosa* and *Hibiscus rosa-sinensis* is used as a juice on the head to protect against fainting. In South America and tropical Africa, including Nigeria, leaves of *A. muricata* are deployed as an ethnomedicine against tumors and cancer. In addition, the anti-inflammatory, hypoglycemic, sedative, smooth muscle relaxant, hypotensive and antispasmodic effects are also attributed to the leaves, barks and roots of *A. muricata*. In addition to ethnomedicinal uses, the fruits are widely employed for the preparation of beverages, candy, ice creams, shakes and syrups[18].

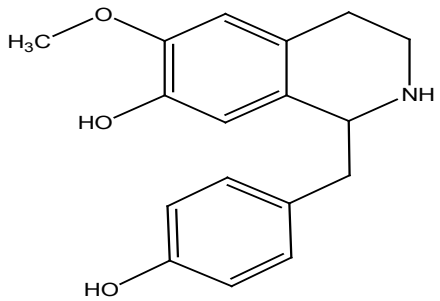
4. Phytochemical Study of *Annona* Species

Annona squamosa L is reported to contain glycoside, alkaloids, saponins, flavonoids, tannins, carbohydrates, proteins, phenolic compounds, phytosterols, amino acids. The different chemical constituents inaccessible from leaves, stems and roots of the plant counting anonaine, aporphine, coryeline, isocorydine, norcorydine, glaucine. Leaves contains 4-(2-nitro-ethyl 1)-1-6-((6-o-β-Dxylopyranosy1-β-D-glucopyranosyl)-oxy)benzene, Anonaine, Benzyltetrahydroisoquinoline, Borneol, Camphene, Camphor, car-3-ene, Carvone, β Caryphyllene, Eugenol, Farnesol, Geraniol, 16-Hetriacontanone, Hexacontanol, Higemamine, Isocorydine, Limonine, Linalool acetate, Menthone, Methyl anthranilate, Methylsalicylate, Methylheptenone, p-(hydroxybenzyl)-6,7-(2-hydroxy,4-hydro) isoquinoline, n-Octacosanol, a Pinene, b-Pinene, Rutin, Stigmasterol, β-Sitosterol, Thymol and n-Triacontanol. Alkaloids, proteins and amino acids are absent in the leaf extract. [19] A lot of phyto-constituents were recognized from different parts of *A. reticulata*. The leaves contain secondary metabolites like alkaloids, steroids, flavonoids, tannins, glycosides, phenolic compounds, amino acids, carbohydrates and proteins.

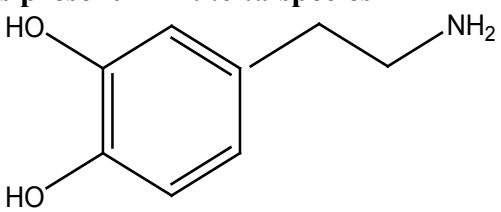
The stem bark contains tannins; alkaloid and phenolic compounds while the root contains acetogenin, alkaloids, flavonoids, tannins, carbohydrates and proteins. The plant was also originate to be rich in minerals like Ca, P, K, Mg, Na, Cl, S, Mn, Zn, Fe, Cu, Se, Co, Ni and Cr.[6] Some phytochemicals of pharmacological significance were characterized including kaurane and kaurene diterpenoids isoquinoline, benzylisoquinoline, aporphine, pyrimidine carboline alkaloids, dopamine and bioactive acetogenins.[20]

Additional investigation have provided us by three antimalarial alkaloids all of them exhibit moderate activity alongside chloroquine sensitive strain (D10) and a chloroquine resistant strain (Dd2) of *Plasmodium falciparum*. [21] The presence of different phytoconstituents like steroids and triterpenoids, alkaloids, glycosides, flavonoids were detected in the plant *Annona reticulata*. [9]

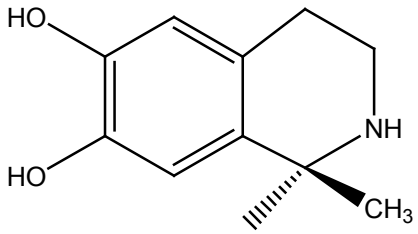
Table 1. Chemical constituents present in *Annona* species



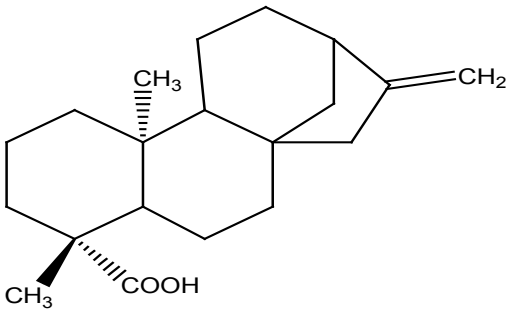
Coclaurine



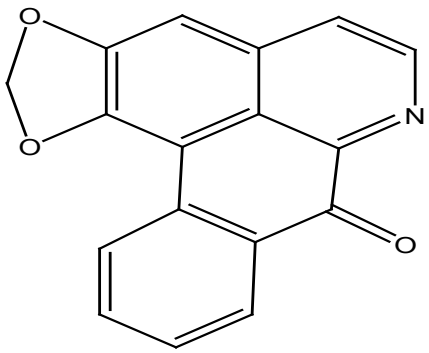
Dopamine



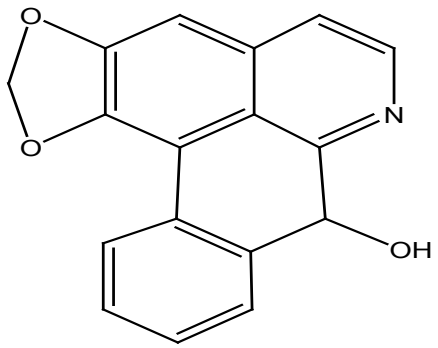
Salsolinol



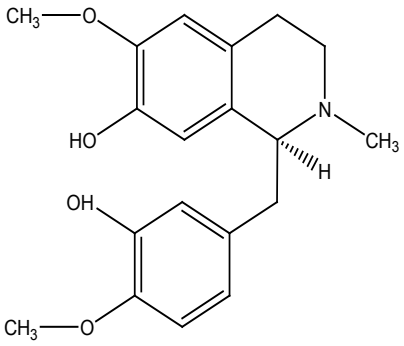
Diterpenes (e)-kau-16-en-19-oic acid



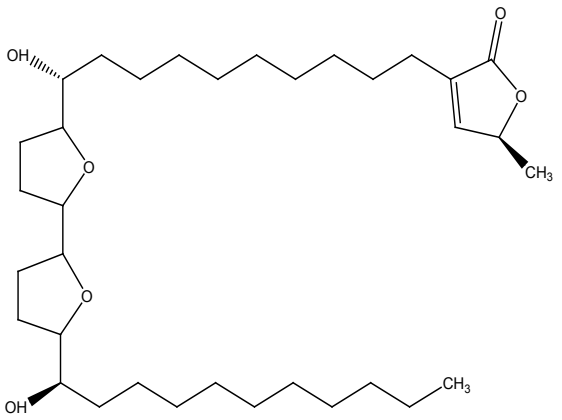
Liriodenine



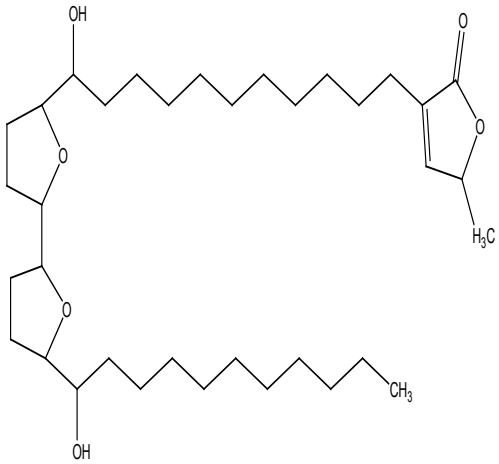
Norushinsunine



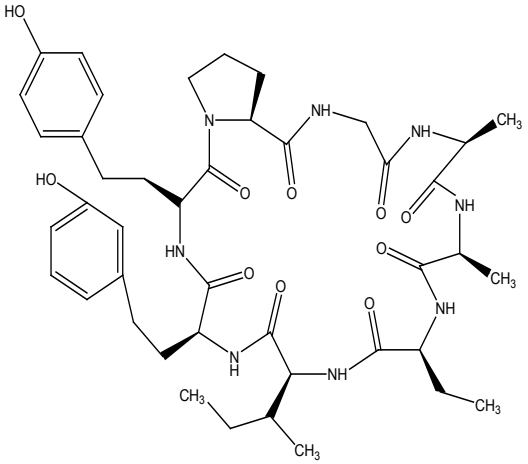
Reticuline



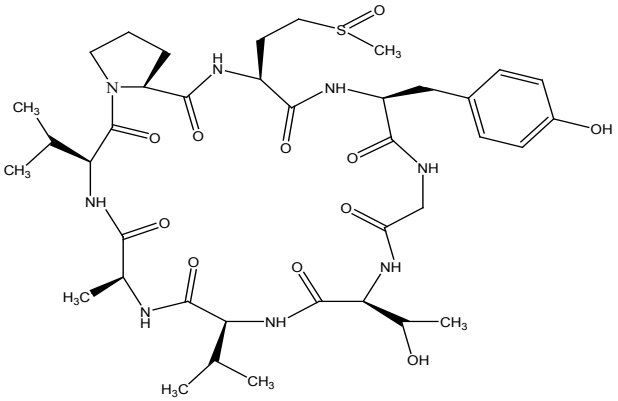
Acetogenin



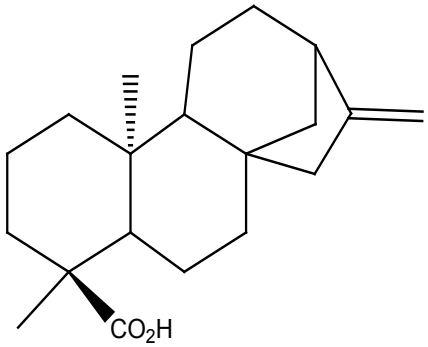
Acetogenin neoannonin



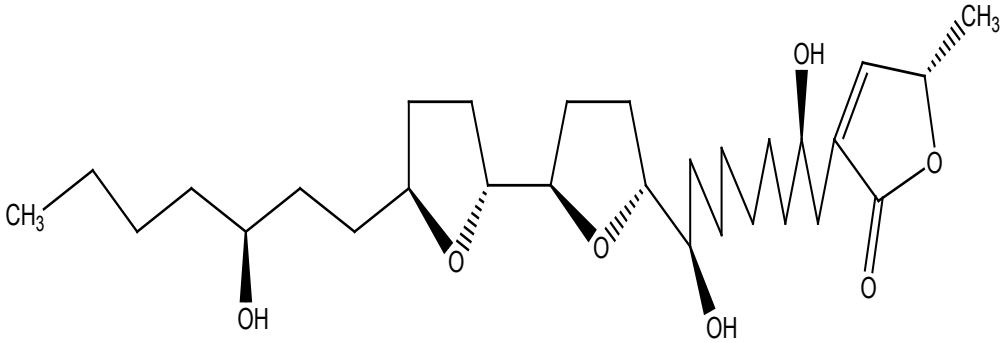
Cycloreticulin-A



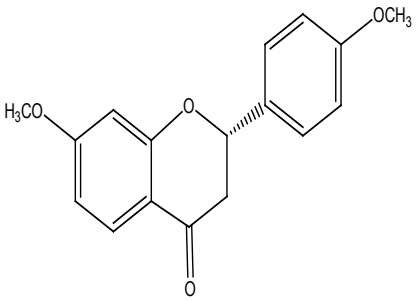
Cycloreticulin-B



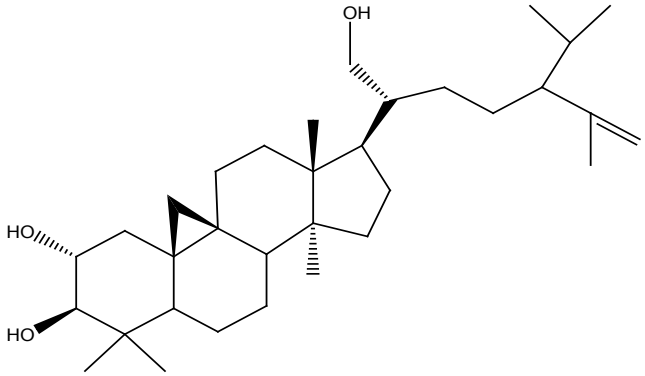
Kaurenoic acid



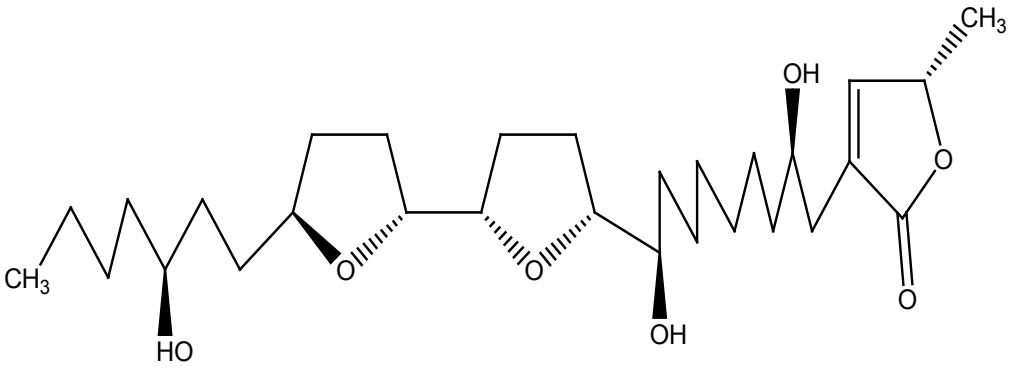
Bullatacin



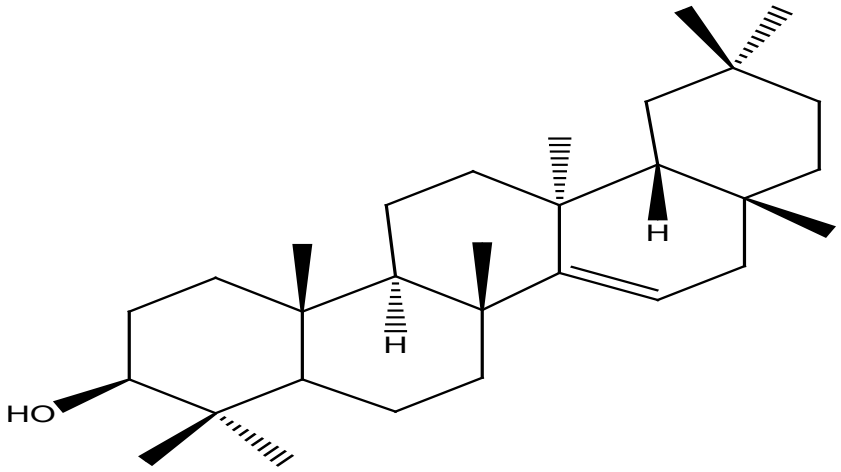
(2s)-di-o-methylquiritigenin



Annonaretin-A



Rolliniastatin



Taraxerol

5. Reported Pharmacological Activity

5.1 Antidiarrhea and Antiulcer Activity

The methanolic extract of *A. muricata* fruit showed 58.38% inhibition of diarrhea at a dose of 400 mg/kg body weight in Swiss albino mice[22]. 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 [23]. Therefore, antidiarrhea activity in *A. muricata* and *A. senegalensis* has been scientifically proven. *Helicobacter pylori* is the major etiological agent of chronic active gastritis and peptic ulcer disease. The traditional use of water-based *A. cherimola* as antiulcer had a long history. A study showed that the methanol leaf/stem extract of *A. cherimola* is better than the water extract with the indicated MIC value of methanol extract amounting to <15.6 µg/ml and MIC value of 250 µg/ml for water extract [24]. 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% [25]

5.2 Antipyretic Activity

The crude aqueous extract of leaves of *A. reticulata* has been screened for antipyretic activity at dose of 200 mg/kg and 400 mg/kg, respectively hyperpyrexia induced by injecting 20% aqueous suspension of Brewer's yeast subcutaneously in rats.[5] Rats showing 0.5^0C-1^0C rise or more in rectal temperature after 18 hr of injection were separated and selected for the study. The results produced by the extract were compared to the standard drug, paracetamol at a dose 150 mg/kg of body weight. Overall study showed that extract of leaves of *A. reticulata* has significant antipyretic activity. [26]

5.3 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 [27]. 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.[28]

5.4 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 EC50 value of barks amounting to 90

mg/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 [29]. On the ORAC method testing of several alkaloid isolated from the bark of *A. salzmannii,* asimilobine was found to be the most active with ORAC value of 2.09 relative Trolox equivalents [30]

5.5 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[31]. 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 ED50 value of >5µg/mL of P-388 cell and ED50 value of 0.6 µg/mL of KB-V1 cell with vinblastine (1 µg/mL) [32] In other plants, anticancer activity was shown by cytotoxicity test with IC50 value of 27.2 µg/mL for *A. pickelii* leaf essential oil, 89.7 µg/mL for *A. salzmannii* leaf essential oil [30] and 1.36 mg/mL for *A. muricata* leaf. [33]

5.6 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. ambotay* also had antibacterial activity with diameter of 10 mm and 9 mm, respectively.[34] 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* [35]. 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 [36]. 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* [37] 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* [38]

5.7 Antitumor Activity

Cancer is the leading cause of death worldwide. In recent years, researches have emphasized on the anti-tumor actions of seeds, per carp and bark of herbs, and active plants chemicals have been identified for their anti-cancer properties.[39] The defatted seed of *Annona reticulata* was screened for the antitumor activity. The extract was of aqueous and organic solvent.[40] The effect of aqueous and organic extracts from defatted seeds of *A. squamosa* was studied on a rat histolytic tumor cell line AK-5. Both the extracts caused significant apoptoic tumor cell death with enhance caspase-3 activity. Down regulation of antiapoptotic genes Bcl-2 and Bclxi and enhance the generation of intracellular ROS, which correlated well with the decreased levels of intracellular GSH. In addition DNA fragmentation and annexin–V staining confirmed that the extracts induced apoptosis in tumor cells through the oxidative stress. Aqueous extracts of *A. squamosa* seeds possessed significant antitumor activity in vivo against AD-5 tumor.[41]

5.8 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%.[42] The essential oil from the leaves of *A. sylvatica* at doses of 20 mg/kg and 200 mg/kg showed 19% and 27% inhibition [43]. These results can be used in the development of herbal anti-inflammatory medicine**.**

5.9 Cytotoxic Activity

Annonaceous acetogenins a new class of compounds that have been reported to have potent pesticidal, parasiticidal, antimicrobial, cell growth inhibitory activities. In this study, organic and aqueous extracts from the defatted seeds of *Annona reticulata* (custard apple) were tested on different human tumor cell lines for antitumoral activity. While organic and aqueous extracts induced apoptosis in MCF-7 and K-562 cells they fails to do so in COLO-205 cells. Treatment of MCF-7 and K-562 cells with organic and aqueous extracts resulted in nuclear condensation, DNA fragmentation, induction of reactive oxygen species (ROS) generation and reduced intracellular glutathione levels.

In addition down regulation of Bcl-2 and PS externalization by Annexin–V staining suggested induction of apoptosis in MCF-7 and K-562 cells by both the extracts through oxidative stress. On the contrary, COLO-205 cells showed only PS externalization but no change in ROS and glutathione levels. These observations suggest that the induction of apoptosis by *A. reticulata* extracts can be selective for certain types of cancerous cells. [44] Two new compounds have been isolated and were evaluated for the above activity. The extract of seed was used for the isolation of the compound. The study was carried out against HCT, human lung carcinoma (A-549), human breast carcinoma (MCF-7), and human prostate adenocarcinoma (PC-3) with adriamycin as positive standard using MTT method.[21]

5.10 Analgesic and CNS depressant

Petroleum ether, ethyl acetate and methanol extracts of *A. reticulata* bark showed significant analgesic activity. Extracts were prepared by successive solvent extraction process. The percentage yields of extracts obtained were petroleum ether 2.3% w/w, ethyl acetate 5.58% w/w and methanolic 13.13% w/w. Analgesic activity was carried out by the hot-plate method whereas central nervous system depressant activity was assessed using locomotor activity assay and pentobarbitone sleeping time test. For both the studies swiss albino mice of either sex weighing 20e25 g were selected. Extract at a dose of 100 mg/kg was used for both studies. Pentazocin lactate injection 20 mg/kg intraperitoneally used as standard for analgesic activity.

Locomotor activity was evaluated using actophotometer where diazepam 2 mg/kg intraperitoneally was used as standard. Sleep was induced by pentobarbitone sodium at 40 mg/kg in the mice and the time interval between losing and regaining of righting reflex was measured. The phytochemical study showed presence of terpenes and steroids in petroleum ether extract, alkaloids and flavonoids in ethyl acetate extract while tannins, flavonoids and glycosides were observed in methanol extract. The petroleum ether extract treated mice showed highest increase in reaction time and significant reduction in the locomotor activity. Also petroleum ether extract potentiated pentobarbitone sodium induced sleeping time. Significant central analgesic activity was exhibited by the extracts in hot plate method. All extracts exhibited mild to moderate central nervous system depressant activity which might be due to increased concentration of GABA in brain. [45]

6. Conclusion

In Asia, *Annona* species are very popular ethnomedicine to the local healers. A lot of pharmacological studies have been carried out with different species of *Annona*. Amongst all medicinal properties of *Annona* species, their antioxidant and cytotoxic activity is very important for establishing ayurvedic drug. The reported pharmacological activities of different *Annona* species suggested the presence of valuable bioactive compounds. Therefore, extensive research should be necessary in the area of isolation and characterization of the compound from that medicinally renewed plant species of *Annona* for the purpose of new drug development.

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Conflicts of interest

The authors declare no conflicts of interest.

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