International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3125-3131 www.ijprajournal.com ISSN: 2249-7781

Annona Muricata: A Compendious Review

Khadeeja Shahana*, Karunakar Hegde
Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India-574143

Submitted: 14-06-2023 Accepted: 24-06-2023

ABSTRACT
Annona muricata, often known as graviola or soursop, is a member of the annonaceae family. It is a medicinal herb that has been used for millennia to heal numerous human diseases. The presence of essential active components in plants has sparked tremendous scientific interest in the biological actions of these compounds. Phytochemical research was conducted on various sections of Annona muricata. 212 secondary metabolites, including acetogenins, alkaloids, phenolic compounds, megastigmanes, flavanol triglycosides, cyclopeptides, and essential oils, have been isolated and identified to date. Diabetes, malaria, cancer, ulcer, inflammatory disease, hypertension, bacterial and viral infection have all been treated with Annona muricata. The goal of this review is to compile existing data on the phytoconstituents and biological activities of Annona muricata leaves.
KEYWORDS: Annona muricata, phytochemistry, antioxidants, inflammatory, pharmacological activities

I. INTRODUCTION

Medicinal plants are considered as the basis for health preservation and care worldwide. Chronic degenerative diseases (diabetes, cardiovascular and cancer) have reached epidemic proportions and are considered as a serious health problem; therefore, the treatments of these diseases are of clinical importance. This past decade has obviously witnessed a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries, with these herbal remedies being available not only in drug stores, but now also in food stores and supermarkets. Herbal medicines are, therefore, often viewed as a balanced and moderate approach to healing and individuals who use them as home remedies and over-the-counter drugs spend huge amount of money on herbal products. [1] Since time immemorial, in search for rescue for their disease, people looked for drugs in nature. The traditional use of medicinal plants can lead to the discovery of new potent botanical agents in the treatment of several diseases. In spite of the development of pharmacological agents for the treatment of chronic diseases, the use of medicinal plants continues to flourish. [2]

Annona muricata L. is a species of the Annonaceae family that has been widely studied in the last decades due to its therapeutic potential. The medicinal uses of the Annonaceae family were reported long time ago, and since then, this species has attracted the attention due to its bioactivity and toxicity. Annona muricata is widely known as soursop due to the sour and sweet taste of its fruit. It is also known as prickly custard apple due to its taste. Graviola can be found in many parts of the tropical and subtropical parts of the world, including some parts of the Americas, Asia and Africa. The tropical plant is characterized as an evergreen and flowering tree that can stand up to 8 metres tall and that produces edible fruits. [3]Annona muricataderived preparations have been utilized to treat numerous ailments such as diabetes, coughs, skin diseases, and cancers. Annona muricata is the most prevalently used herbal remedy in the treatment of most cancers. In addition, it has been mentioned as an antimicrobial, anti-diabetic, anti-inflammatory, antiprotozoan, antioxidant, insecticide, larvicide, and anticancer. [4]

TAXONOMY AND DISTRIBUTION

Annona muricata is commonly known as soursop, graviola, sirsak, guanabana and paw-paw. This plant has the taxonomic classification of the domain Eukaryotes, the kingdom of Plantae, the division of Magnoliophyta, the class of Magnoliopsida, the order of Magnoliales, the family of Annonaceae, the genus of Annona and the species of Annona muricata L.[5] The accepted full name of this species is Annona muricata L. with other synonyms such as Annona muricata var. borinquensis Morales, Annona muricata f. mirabilis, Annona bonplandiana Kunth, Annona cearaensis Barb. Rodr, Annona macrocarpaand Guanabanus muricatus. The Annonaceae family consists of approximately 130

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3125-3131 www.ijprajournal.com ISSN: 2249-7781

genera and 2300 species, while the genus Annona comprises over 70 species among which Annona muricata is the most widely grown. [6]

The soursop tree is about 5–10 m tall and 15–83 cm in diameter with low branches. It tends to bloom and fruit most of the year, but there are more defined seasons depending on the altitude. It is distributed in the tropical regions of Central and South America, Western Africa and Southeast Asia, at altitudes below 1200 m above sea level, with temperatures between 25 and 28 °C, relative humidity between 60 and 80%, and annual rainfall above 1500 mm. The soursop fruit is an edible collective ovoid berry, dark green in color. Its average weight is 4 kg in some countries, but in Mexico, Venezuela and Nicaragua it ranges between 0.4 and 1.0 kg. Each fruit may contain 55–170 black seeds when fresh and they turn light brown when dry. The flesh is white and creamy with a characteristic aroma and flavor. [7]

VERNICULAR NAMES

Hindi – Hanuman phal.
Kannada – Mulluramphala.
Tamil – Mullu-sitha-pazham.
Malayalam – Mullaatha.
Harari – Amba Shoukh.

DESCRIPTION

TREE: Annona muricata is a slender, evergreen tree 5-10 m in height and 15 cm in diameter with straight trunk, smooth bark which turns into grey-brown or dull grey, rough and fissured with age. At first branches grow ascending with the crown forming an inverted cone and later spreading.

LEAVES: Alternate, 7.6 – 15.2 cm long, 2.5 – 7.6 cm wide, leathery, obovate to elliptic, glossy on top, glabrous on underside; green on top, paler and dull on under side with fine lateral nerves; a strong, pungent odour; petioles short, 3 – 10 mm long

FLOWERS: Terminal or lateral, large; stalks stout, green, 1.3 – 1.9 cm long; 3 sepals, minute, inconspicuous, broad, green, 3mm long, triangular; petals yellowish – green, outer petals larger, 3 inner petals, stamens numerous,, each with 1 ovule; pistils white; sticky stigma.

FRUIT:14-40 × 10-18cm, weighing upto 7kg, ovoid, heart shaped, an oblong syncarp composed of numerous united pistils; often assymetric due to incomplete fertilization of the ovules; epidermis often shining, dark green, with short, fleshy spines covering each carpel; pulp white, fiborous and juicy; seeds shiny, dark brown or black, oblong, upto 2cm long, 0.7 cm wide.[8]

PHYTOCONSTITUENTS

Phytochemical studies reveal that approximately more than 212 compounds have been isolated from Annona muricata in which predominant secondary metabolites are acetogenins, alkaloids, phenolic compounds and others. Acetogenins are class of polyketide characterized by linear 32- or 34-carbon chains containing oxygenated functional groups including hydroxyls, ketones, epoxides, tetrahydrofurans and tetrahydropyrans.[9] Other phytoconstituents such as flavonoids, flavanol glycosides, tannins, cardiac glycosides and steroids present have been reported for their biological activities in the prevention and management of human diseases. Flavonoids and phenolic compounds have been reported to possess antioxidant, anti-inflammatory, anti-allergenic, anti-cancer and hepatoprotective activities.[10]

It is also reported the presence of rutin and narringenin while vanillin, gallic acid and eugenol were present in minor fractions. Rutin is a rhamnoglucoside of the flavonoid quercetin which is the principal compound of Annona muricata leaves. It is an effective inhibitor of dihydrofolate reductase and shows anti-viral, anti-cancer, anti-inflammatory and cardiovascular protective activities. Quercetin and gallic acid are reported to be responsible for the antioxidant capacity of the plant. [11]

PHARMACOLOGICAL ACTIVITIES

ANTIBACTERIAL ACTIVITY

Annona muricata leaves are potential and newly effective drug for bacterial infections including multi-drug resistant bacteria. The methanol, aqueous and n-hexane extracts of Annona muricata leaves was effective against Escherichia coli, Staphylococcus aureus and Moraxella catarrhalis. The n-hexane extract of Annona muricata leaves exhibited highest inhibitory action against Enterococcus faecium and Acinetobacter baumarii. The sensitivity of this plant could be traced down to its strong ethnomedical foundation where many countries such as Peru, Brazil and Togo use Annona muricata for treatment of skin infections, diarrhoea, dysentery, sores, fever, cold and internal ulcers. [12]

ANTICANCER ACTIVITIES

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3125-3131 www.ijprajournal.com ISSN: 2249-7781

Plenty of studies report shows the antiproliferative effects of different extracts of the plant is used as complementary medicines. The isolated Annonaceous acetogenins(AGEs) from the plant is reported to induce cell cytoxicity by inhibiting the mitochondrial complex 1. It is revealed that extracts of Annona muricata inhibit the proliferation of breast cancer cells by inducing cytotoxic activity in lung cancer, breast cancer, liver cancer, pancreatic cancer, prostate cancer and colon cancer.[13] The n-hexane extract of Annona muricata leaves antiproliferative against pancreatic cancer cell line, Capan 1. Annona muricata also inhibited the motility and invasion of PC cells by downregulating the mucin MUC4. Several bioactive compounds have been tried as adjuvants to existing therapy for treating and preventing hormone-refractory pancreatic cancer, but no clinical success has been found.CRC (colorectal carcinoma) is the third most common cause of cancer-related fatalities. In the COLO-205 (human colon adenocarcinoma) cell line, the Annona muricata leaf extract also showed anticancer properties by increasing the proapoptotic protein caspase-3. The ability of a leaf fraction from Annona muricata to induce caspase 3 expression in cells cultivated from WHO stage III nasopharyngeal carcinoma biopsy tissue was studied. The plant extracts have been shown to have a cytotoxic impact on hepatic cancer cells, hinting that they could be employed as a hepatic cancer treatment. The HepG2 cell line was shown to be inhibited in growth and viability after being incubated with an ethanol extract of Annona muricata. The acetogenins and other secondary metabolites, such as alkaloids are major compounds which have shown to inhibit cancer growth. The molecular mechanisms of different components of graviola extract regulate metastasis, proliferation, apoptosis, and cell signaling. The phytoconstituents present allure the concept of employing these components in a tailored method to strengthen our arsenal against cancer. [14]

ANTIVIRAL ACTIVITY

The bioactive compounds responsible for antiviral efficacy have also shown to be selectively cytotoxic while inhibiting tumorigenic cell growth without affecting the normal cell growth. Annona muricata was shown to exhibit antiviral activity against Herpes simplex virus-1 and Herpes simplex virus-2, human papilloma virus, hepatitis C virus, dengue virus type 2, human immunodeficiency virus-1. As per study it is revealed that Annonaceous aceous acetogenins show a good inhibition activity against SARS-CoV-2 spike protein as per the Molecular Docking and MD simulation. Cis-Annonacin was identified to be the most potent acetogenin with a low binding energy and greater hydrogen bond formation potential. [15]

ANTI-DIABETIC ACTIVITY

Many herbs and plant products have been shown to have hypoglycemic action. Various morphological parts of Annona muricata have been reported to be useful as effective remedies against diabetes. It act by several mechanisms such as stimulating insulin secretion, increasing repair or proliferation of β-cells and enhancing the effects of insulin and adrenalin. It is studied that streptozotocin induced diabetes mellitus in wistar rats have shown significant decrease in blood glucose level after administration of methanolic extract of Annona muricata leaves. [16] It promotes better glycemic control, normalizes lipid parameters, stimulates insulin secretion and action, increases body weight and improves the morphology of pancreas and liver. [17]

ANTI-INFLAMMATORY AND ANTI-ARITHRITIC ACTIVITY

Annona muricata L. is one of the many plant extracts that have been explored owing to their anti-inflammatory and anticancer effects. The in vitro study conducted revealed that Annona muricata leaf extract possessed anti-inflammatory activity as it inhibited the inflammatory mediators, TNF-α, IL-1β, IL-6 and nitric oxide. [18] It is also proved effective in wound healing potential of the extract on rats with excisional wound. [19] The in vivo study of anti arithritic activity in complete Freund's adjuvant (CFA)-induced arithritis showed that the oral administration of ethanolic extract of Annona muricata leaves reduced edema in dose dependent manner. It also contributed to suppression of pro-inflammatory cytokines by suppressing TNF-α and IL-β expression in local tissue thus showing anti – arithritic activity.[20]

ANTI-OBESITY ACTIVITY

The in-vivo study of anti-obesity in Annona muricataplant extract was determined on FTO gene expression in high fat diet induced obesity in rats. The expression of FTO gene was up-regulated in high fat diet induce obese rats (HFD) when compared to the control group.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3125-3131 www.ijprajournal.com ISSN: 2249-7781

Treatment of obese rats with Annona muricata (200 mg/kg) for 21 days showed significant down-regulation of FTO gene expression when compared to obese untreated rats. The down-regulation of FTO by phytocompounds in Annona muricata is an indication that they are inhibitors of FTO. The mRNA expression of STAT-3 gene was down-regulated in HFD rats. The results of the in vivo and in silico study suggests that Annona muricata extract possess excellent anti-obesity property and its mechanism of action is probably through the down-regulation of FTO and up-regulation of STAT-3 genes leading to reduction in food intake. This was probably possible due to the vast enormity of phytochemicals in Annonamuricata extract especially the annonioside and annonaine that showed highest binding interaction with FTO from docking experiment relative to other phytochemicals found in Annona muricata. [21]

ANTI-CONVULSANT AND ANXIOLYTIC ACTIVITY

The presence of flavonoids and apomorphinic alkaloids have made Annona muricata most interesting and according to some studies this plant have effects on the central nervous system. Ethnopharmacological study reveals the use of dried leaf infusions of Annona muricata is used to treat anxiety, insomnia, and headaches. [22] The study on ethyl acetate fraction and insoluble ethyl acetate of Annona muricata leaves extracts in PTZ induced mice shows anticonvulsant properties. Tonic incidence decreased with increasing dose, although the ethyl acetate insoluble fraction doses of 100 and 200 mg / kg have the same percentage. To the onset tonic, giving ethyl acetate fraction and insoluble fraction of ethyl acetate at different doses may prolong the onset of tonic or may delay the occurrence of tonic with a significance value of less than 0.05. The parameters used are parameters of onset, incidence, and duration of tonic, time of death and the number of deaths were used to support the conclusion. [23] The study demonstrated that both the aqueous and ethanolic extracts of the leaves and bark of Annona muricata exert an anxiolytic effect on rats which substantiates its traditional use in the management of anxiety. The study was conducted using elevated plus maze (EPM) model and result showed that there were significant increase in mean entries into open arms and mean time spent in open arms. [24]

ANTIHYPERTENSIVE ACTIVITY

Hypertension is a major risk factor for the development of cardiovascular disease, and medications aimed at reducing blood pressure. Annona muricata caused significant dose-dependent reduction in blood pressure without affecting the heart rates. The hypotensive effects were unaffected by atropine, mepyramine, propranolol and l-NAME. Annona muricata leaf aqueous extract significantly relaxed phenylephrine (10–9–10–4 M) and 80 mM KCl induced contractions in endothelium intact and denuded aortic rings and caused a significant rightward shift of the $Ca2^{+}$ dose response curves in $Ca2^{+}$-free Kreb's solution containing 0.1 mM EGTA. The hypotensive effects of Annona muricata are not mediated through muscarinic, histaminergic, adrenergic and nitric oxide pathways, but through peripheral mechanisms involving antagonism of $Ca2^{+}$. [25]

GASTROPROTECTIVE AND ANTI-NOCICEPTIVE ACTIVITY

Peptic ulcer is defined as integrity disturbance of the duodenum or gastric mucosa, which is characterized by mucosal damages. The study suggest that the gastroprotective effects of ethyl acetate extract of Annona muricataleaves (EEAM) against ethanol-induced gastric injury models in rats. Gross and histological features showed the antiulcerogenic characterizations of EEAM. There was significant suppression on the ulcer lesion index of rats pretreated with EEAM. Oral administration of EEAM to rats caused a significant increase in the level of nitric oxide and antioxidant activities, including catalase, glutathione, and superoxide dismutase associated with attenuation in gastric acidity, and compensatory effect on the loss of gastric wall mucus. In addition, pretreatment of rats with EEAM caused significant reduction in the level of malondialdehyde, as a marker for oxidative stress, associated with an increase in prostaglandin E2 activity. Immunohistochemical staining also demonstrated that EEAM induced the downregulation of Bax and upregulation of Hsp70 proteins after pretreatment. Collectively, the present results suggest that EEAM has a promising antiulcer potential, which could be attributed to its suppressive effect against oxidative damage and preservative effect toward gastric wall mucus. [26]
Antinociceptive activity of AML extract was done using acetic acid-induced abdominal writhing in mice, formalin test in rats and hot plate test in

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3125-3131 www.ijprajournal.com ISSN: 2249-7781

mice. The aqueous ethanol extract of Annona muricata leaves showed significant reduction and dose dependent reduction in the abdominal writhes in acetic acid induced writhing test. Similarly when tested with formalin and hot plate test method the aqueous ethanol extract of Annona muricata leaves are found to be effective in antinociceptive activity. Therefore, the results obtained in the antinociceptive tests appear to suggest that AML possesses significant centrally and peripherally mediated antinociceptive properties. The central nociception effect may be mediated via inhibition of central pain receptors, whilst the peripheral nociception activity may be mediated through inhibition of cyclooxygenase and/or lipoxygenase. [27]

HEPATOPROTECTIVE AND JAUNDICE

Liver diseases and jaundice have continued to be a major health problem in the world with most conventional drugs not being adequate for treatment. Conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects. Liver damage and hepatic jaundice were induced in experimental animals by administering CCl4 and acetaminophen after pretreatment with aqueous extract of Annona muricata. Hepatoprotective effect was studied by assaying the activity of serum marker enzymes such as alanine aminotransferase, alkaline phosphatase, cholesterol, and triglycerides while anti-jaundice effect was assayed by measuring serum total bilirubin and indirect bilirubin concentration.The activity of all the marker enzymes registered significant increases in CCl4 and acetaminophen-treated rats, decreases in cholesterol and triglyceride concentration, and increases in total and indirect bilirubin, an indication of hepatic jaundice. Annona muricata at all doses significantly restored liver function toward normal levels which compared well against silymarin control.AMAE possibly possesses antioxidant effect at all doses, as with Silymarin, and deplete pro-oxidants generated by the metabolism of CCl4 attributable to the presence of flavonoids in the aqueous extract. Histopathological analysis of liver sections confirmed biochemical investigations. [28]

ANTI-MALARIAL ACTIVITY

Malaria is a disease caused by Plasmodium species and transmitted by the bite of female Anopheles mosquito. The global strategy for malaria mainly focuses on case management through provision of drugs capable of reducing or eliminating parasites. It is evident based on these findings that the oral administration of Annona muricata aqueous leaf extract (100–1000 mg/kg) to mice for 4 days significantly reduced parasitemia of PbANKA in experimental mice with nontoxicity. The Annona muricata aqueous leaf extract prolonged the MST of the infected mice indicating that it suppressed PbANKA and reduced the overall pathologic effect of the parasite on the infected mice indicating that antioxidant and antimalarial effects of this extract may play a critical role. [29]

TOXICOLOGY

The study shows that consumption of Annona muricata has possible etiology of toxicity. The most abundant acetogenins present in the plant, alkaloids and annonacin were in-vitro toxic to dopaminergic and other neurons. Annonacin was toxic in nanomolar concentration whereas alkaloids were in micromolar. It is shown that high concentration of annonacin present in aqueous extract of fruit juice or leaves can cross blood brain barrier and induce neuronal degeneration of basal ganglia which is observed in atypical parkinsonism. [30]

II. CONCLUSION

Annona muricata is an evergreen plant which attracts greater attention because of high medicinal value in herbal folklore practices and it is distributed almost throughout the world. The leaves of Annona muricatais rich in annonaceous acetogenins. Other phytoconstituents present in Annona muricata involves flavonoid, phenolic compounds, alkaloids and tannins. The antioxidant capacity of these compositions makes it useful in treating cancer, inflammation, diabetes and worms. Hepatoprotective, gastroprotective, anti-nociceptive, malaria, asthma, anti-parasitic, anti-jaundice, wound healing, insecticide and larvicidal. As the major constituents are acetogenins such as annonacin and alkaloids the toxicity of plants are also reported. Currently the research is based on biological activity of plants. Further clinical studies are required to verify and validate the plant extracts safety and toxicity.

REFERENCES

[1]. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring

safety. Frontiers in pharmacology. 2014 Jan 10;4:177.

[2]. Eddouks M, Chattopadhyay D, De Feo V, Cho WC. Medicinal plants in the prevention and treatment of chronic diseases 2013. Evidence-Based Complementary and Alternative Medicine. 2014 Oct;2014.

[3]. Yajid AI, Ab Rahman HS, Wong MP, Zain WZ. Potential benefits of Annona muricata in combating cancer: A review. The Malaysian journal of medical sciences.2018 Feb;25(1):5.

[4]. Rady I, Bloch MB, Chamcheu RC, Banang Mbeumi S, Anwar MR, Mohamed H, Babatunde AS. Anticancer properties of graviola (Annonamuricata): a comprehensive mechanistic review. Oxidative medicine and cellular longevity. 2018 Jul 30;2018.

[5]. Gavamukulya Y, Wamunyokoli F, El-Shemy HA. Annona muricata: Is the natural therapy to most disease conditions including cancer growing in our backyard? A systematic review of its research history and future prospects. Asian Pacific journal of tropical medicine. 2017 Sep 1;10(9):835-48.

[6]. Abdul Wahab SM, Jantan I, Haque MA, Arshad L. Exploring the leaves of Annona muricata L. as a source of potential anti-inflammatory and anticancer agents. Frontiers in pharmacology. 2018 Jun 20;9:661.

[7]. Coria-Téllez AV, Montalvo-Gónzalez E, Yahia EM, Obledo-Vázquez EN. Annona muricata: A comprehensive review on its traditional medicinal uses, phytochemicals, pharmacological activities, mechanisms of action and toxicity. Arabian Journal of chemistry. 2018 Jul 1;11(5):662-91.

[8]. Orwa C, Mutua, Kindt R, Jamnadass R, Anthony. Annona muricata. Agroforestree database: a tree reference and selection guide version 4.0. 2009;1-5.

[9]. Rojas-Armas JP, Arroyo-Acevedo JL, Palomino-Pacheco M, Ortiz-Sánchez JM, Calva J, Justil-Guerrero HJ, Castro-Luna A, et al. Phytochemical Constituents and Ameliorative Effect of the Essential Oil from Annona muricata L. Leaves in a Murine Model of Breast Cancer. Molecules. 2022 Mar 10;27(6):1818.

[10]. Olasehinde OR, Afolabi OB, Owolabi OV, Akawa AB, Omiyale OB. GC–MS analysis of phytochemical constituents of methanolic fraction of Annona muricata leaf and its inhibition against two key enzymes linked to type II diabetes. Scientific African. 2022 Jul 1;16:e01178.

[11]. Balderrama-Carmona AP, Silva-Beltrán NP, Gálvez-Ruiz JC, Ruíz-Cruz S, Chaidez-Quiroz C, Morán-Palacio EF. Antiviral, antioxidant, and antihemolytic effect of Annona muricata L. leaves extracts. Plants. 2020 Nov 26;9(12):1650.

[12]. Akanji OC. Antibacterial activity of Annona muricata leaves' extracts. International Journal of Frontier Research in Science. 2023;2(1):024-8.

[13]. Syed Najmuddin SU, Romli MF, Hamid M, Alitheen NB, Nik Abd Rahman NM. Anti-cancer effect of Annona Muricata Linn Leaves Crude Extract (AMCE) on breast cancer cell line. BMC complementary and alternative medicine. 2016 Dec;16:1-20.

[14]. Ilango S, Sahoo DK, Paital B, Kathirvel K, Gabriel JI, Subramaniam K, Jayachandran P. A review on Annona muricata and its anticancer activity. Cancers. 2022 Sep 19;14(18):4539.

[15]. Prasad SK, Pradeep S, Shimavallu C, Kollur SP, Syed A, Marraiki N, Egbuna C, et al. Evaluation of Annona muricata acetogenins as potential anti-SARS-CoV-2 agents through computational approaches. Frontiers in Chemistry. 2021:1281.

[16]. Aderibigbe K, Komolafe OA, Adewole OS, Obuotor EM, Adenowo TK. Anti-hyperglycemic activities of Annona muricata (Linn). African Journal of Traditional, Complementary and Alternative Medicines. 2009;6(1).

[17]. Alwan IA, Lim V, Abd Samad N, Widyawati T, Yusoff NA. Effect of Annona muricata L. on metabolic parameters in diabetes mellitus: a systematic review. Current Research in Nutrition and Food Science Journal. 2020 Apr 25;8(1):01-11.

[18]. Laksmitawati DR, Prasanti AP, Larasinta N, Syauta GA, Hilda R, Ramadaniati HU, Widyastuti A, et al. Anti-inflammatory potential of gandarusa (Gendarussa vulgaris Nees) and soursop (Annona

muricata L) extracts in LPS stimulated-macrophage cell (RAW264. 7). Journal of Natural Remedies. 2016 Aug 18:73-81.

[19]. Elmas O, Sahin HH, Guven B, Abuzaid MM, Elshami W, ALMisned G, Zakaly HM, et al. A focusing study on radioprotective and antioxidant effects of Annona muricata leaf extract in the circulation and liver tissue: Clinical and experimental studies. Open Chemistry. 2022 Jan 1;20(1):920-8.

[20]. Moghadamtousi SZ, Fadaeinasab M, Nikzad S, Mohan G, Ali HM, Kadir HA. Annona muricata (Annonaceae): a review of its traditional uses, isolated acetogenins and biological activities. International journal of molecular sciences. 2015 Jul 10;16(7):15625-58.

[21]. Elekofehinti OO, Lawal AO, Ejelonu OC, Molehin OR, Famusiwa CD. Involvement of fat mass and obesity gene (FTO) in the anti-obesity action of Annona muricata Annonaceae: in silico and in vivo studies. Journal of Diabetes & Metabolic Disorders. 2020 Jun;19:197-204.

[22]. Souza DO, dos Santos Sales V, de Souza Rodrigues CK, de Oliveira LR, Lemos IC, de Araújo Delmondes G, Monteiro ÁB, et al. Phytochemical analysis and central effects of Annona muricata Linnaeus: possible involvement of the gabaergic and monoaminergic systems. Iranian Journal of Pharmaceutical Research: IJPR. 2018;17(4):1306.

[23]. Rohadi D, Bachri MS, Nurani LH. Anticonvulsant effect of ethyl acetate fraction and unsolved ethyl acetate fraction from sirsak leaf (Annona muricata, L.) On pentylentetrazol induced in mice. Proceeding of International Safety Management of Central Cytotoxic Reconstitution May 25th. 2013:171.

[24]. Ohemeng KA, Doe P, Pappoe MA, Gordor DT, Adubea Y, Amaglo SM, Prempeh JM. Evaluation of the anxiolytic effects of the aqueous and ethanolic extracts of the leaves and bark of Annona muricata using the elevated plus maze test.

[25]. Nwokocha CR, Owu DU, Gordon A, Thaxter K, McCalla G, Ozolua RI, Young L. Possible mechanisms of action of the hypotensive effect of Annona muricata (soursop) in normotensive Sprague–Dawley rats. Pharmaceutical biology. 2012 Nov 1;50(11):1436-41.

[26]. Moghadamtousi SZ, Rouhollahi E, Karimian H, Fadaeinasab M, Abdulla MA, Kadir HA. Gastroprotective activity of Annona muricata leaves against ethanol-induced gastric injury in rats via Hsp70/Bax involvement. Drug design, development and therapy. 2014 Oct 28:2099-111.

[27]. Hamid RA, Foong CP, Ahmad Z, Hussain MK. Antinociceptive and anti-ulcerogenic activities of the ethanolic extract of Annona muricata leaf. Revista Brasileira de Farmacognosia. 2012;22:630-41.

[28]. Arthur FK, Larbie C, Woode E, Terlabi EO. Evaluation of hepatoprotective effect of aqueous extract of Annona muricata (Linn.) leaf against carbon tetrachloride and acetaminophen-induced liver damage.

[29]. Somsak V, Polwiang N, Chachiyo S. In vivo antimalarial activity of Annona muricata leaf extract in mice infected with Plasmodium berghei. Journal of pathogens. 2016 Mar 22;2016.

[30]. Lannuzel A, Höglinger GU, Champy P, Michel PP, Hirsch EC, Ruberg M. Is atypical parkinsonism in the Caribbean caused by the consumption of Annonacae?. InParkinson's disease and related disorders 2006 (pp. 153-157). Springer Vienna.