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Annona Muricata (Linn.) Acetogenins as Potent Anti-Breast Cancer Agents

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Review Article

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Abstract

Breast cancer is the most common type of cancer in women, globally. In India, it has been ranked number one with regard to cancer incidence in both men and women. Phytotherapy has been extensively considered against cancer, and *Annona muricata* is one such plant species that has gained scientific interest for decades. The acetogenins, a class of phytocompounds exclusively to the *Annonaceae* family of plant kingdom, are known contributors towards this biomedical significance of the *A. muricata*. In this review, we have identified those *A. muricata* acetogenins that exhibit anti-breast cancer activity.

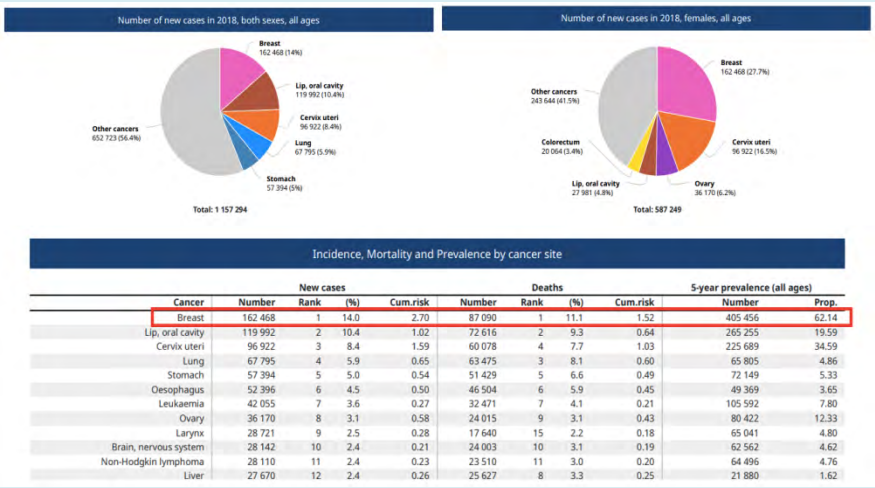
Keywords: *Annona Muricata*; Acetogenins; Anti-Breast Cancer; *Annonaceae*

Introduction

Breast cancer is the most common cancer in India, accounting to 27.7% of all cancers in women. As a matter of fact, Breast cancer is ranked number 1, with 14% incidence among all the other types of cancer incident in both Indian men and women (Figure 1). It is also regarded the leading cause of death due to cancer in women [1]. In India, 50% of the women diagnosed of breast cancer, die of it. There has been a rise, globally, in the incidence and mortality rates due to breast cancer [2-6]. Under-reporting of breast cancer has been documented in several studies conducted, implying that the actual numbers are higher than reported owing to the lack of public awareness. The implications drawn at this juncture indicate that the incidence of breast cancer is occurring at an alarming rate and there has been a considerable shift in the average age of development of breast cancer in India, i.e. From 50-70 to 30-50 years [7]. Nonetheless, indicating that the utmost prominence is to be provided for breast cancer research as such a drastic age shift towards the youth of a woman's life can be damaging the interests at the personal as well as the national levels. This rise in incidence and mortality rates is mainly attributed to a range of factors: (a) Change in lifestyle, including an increase in sedentary working patterns and exposure to environmental risk factors; (b) genetic history, wherein risk of a development of breast cancer is thrice the normal circumstances in the case of women with mothers having breast cancer and about 5% of reported cases are hereditary; (c) Tobacco smoking and substance abuse; (d) Maternity factors, like first child birth at a later age, fewer children and shorter breast-feeding duration; (e) Early menarche and delayed menopause [8]. Lack of health education and awareness is also an important factor to consider in the Indian scenario. With delayed appearance and diagnosis, the chances of survival are limited. Indicating an immediate requirement of affordable and highly effective therapeutic agents for the treatment of breast cancer in its advanced metastatic stages [9]. Consequently, the pivotal role played by medicinal plants has led to their consideration in health preservation and care, worldwide. Resulting in

various researches focusing on recognizing plants with anticancer properties.

Over the last decade, various findings have established the therapeutic abilities of *Annona muricata (A. muricata),* with the bioactivity as well as toxicity of the species gaining an attention. The plant has been used widely for its bioactive metabolites due to curative properties. *A. muricata* plant extracts are known to contain phytocompounds which are particularly effective against cancer cells.



	New cases				Deaths				5-year prevalence (all ages)	
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop.
Breast	162 468	1	14.0	2.70	87 090	1	11.1	1.52	405 456	62.14
Lip, oral cavity	119 992	2	10.4	1.02	72 616	2	9.3	0.64	265 255	19.59
Cervix uteri	96 922	3	8.4	1.59	60 078	4	7.7	1.03	225 689	34.59
Lung	67 795	4	5.9	0.65	63 475	3	8.1	0.60	65 805	4.86
Stomach	57 394	5	5.0	0.54	51 429	5	6.6	0.49	72 149	5.33
Oesophagus	52 396	6	4.5	0.50	46 504	6	5.9	0.45	49 369	3.65
Leukaemia	42 055	7	3.6	0.27	32 471	7	4.1	0.21	105 592	7.80
Ovary	36 170	8	3.1	0.58	24 015	9	3.1	0.43	80 422	12.33
Larynx	28 721	9	2.5	0.28	17 640	15	2.2	0.18	65 041	4.80
Brain, nervous system	28 142	10	2.4	0.21	24 003	10	3.1	0.19	62 562	4.62
Non-Hodgkin lymphoma	28 110	11	2.4	0.23	23 510	11	3.0	0.20	64 496	4.76
Liver	27 670	12	2.4	0.26	25 627	8	3.3	0.25	21 880	1.62

Figure 1: Cancer incidence and demographics, in India, as of 2018. (***Source:*** *GLOBOCAN 2018).*

Botanical Description

Annona muricata (Linn.) is a tropical plant variety belonging to the considerably large *Annonaceae* Family. Commonly called *Soursop* in English and *Lakshmanaphala/ Hanumaphala* in India, the *A. muricata* plant is known globally for its use as a traditional medicine as well as refreshment.

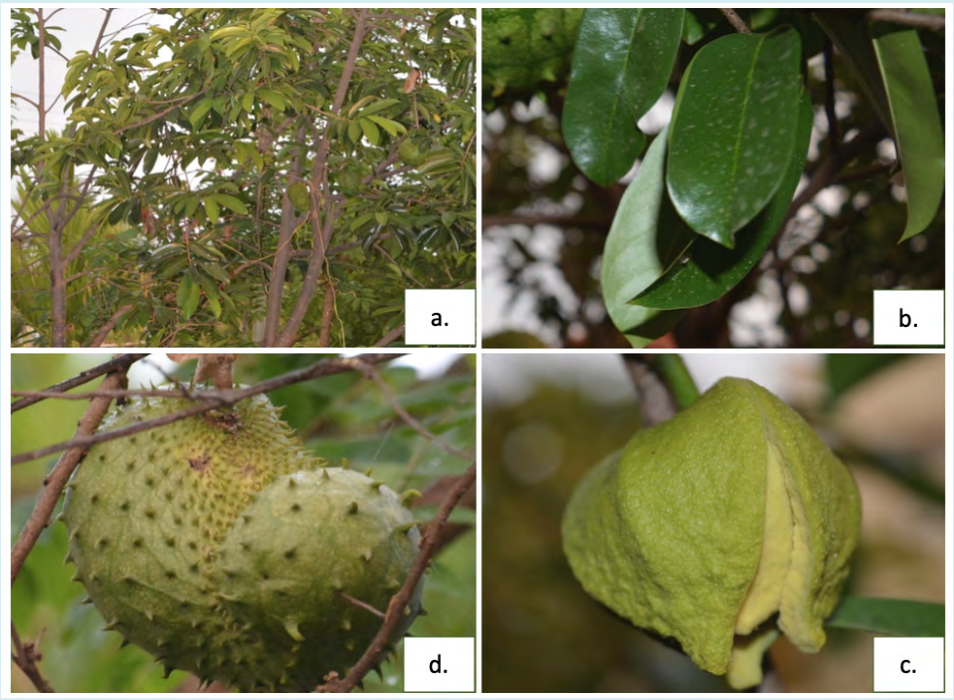


Figure 2: a) *Annona muricata* tree; b) Leaves; c) Flower; d) Fruit (Source: Shashanka K Prasad et al. (2019).

Out of nearly 70 species classified under the genus *Annona*, *A. muricata* has been reported to be the most extensively grown. *A. muricata* trees are relatively small, growing up to 5-10 meters in height and about 15-83 centimeters in breadth. The plant is characterized by its low branches, showy yellow-green flowers, a dull green ovoid berry fruit and dark green leaves (Figure 2) [10,11].

Ethnomedicinal Applications

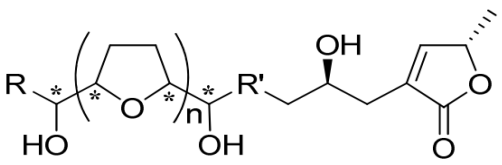
Use of *A. muricata* plant and plant organs in ethnomedicinal practices has been widely reported. Literature suggests that all part of the plant, *viz.* leaves, fruits, barks, roots, and seeds have been extensively used in preparation of traditional medicines for the treatment of a wide range of diseases from fever to cancer [11-13]. Notwithstanding, the numerous traditional uses of *A. muricata* yet remain undocumented, thereby shedding little light on its medicinal benefits [14,15]. The validation of these biomedical significances of *A. muricata* has been carried out since over eight decades now and substantial evidences ascertain the use of the plant in natural medicine. Decoctions of the plant organ phytochemicals have been reported to be widely used as cure for various diseases and disorders [11]. For instance, the *A. muricata* leaf decoction was reportedly used as an analgesic as well as comforting agent in the event of cold, flu, asthma and malaria [13,16], while the fruit juice was consumed to promote lactation, to ease the discomforts arising from diarrhoea, cardiovascular and hepatic disorders, and against intestinal parasites [11]. Furthermore, *A. muricata* has been found to be extensively used in the treatment of torment, respiratory and skin diseases, bacterial infections, hypertension, aggravation, inflammation, neuralgia, rheumatism, cystitis, diabetes and even cancer. In addition, records indicate that *A. muricata* was used as a sedative, smooth muscle relaxant, nervine, and astringent. Recent reports highlight the use of *A. muricata* capsules, concentrates and even the extracts of phytochemicals towards treatment of the major types of cancer [17-20].

Phytochemistry

Nearly 212 phytochemicals have been reported to be present in the *A. muricata* plant [11,13]. Alkaloids, phenolic acids, cyclopeptides, flavonol triglycosides, cyclopeptides, megastigmanes and essential oils constitute a major portion of the phytochemical composition. Meanwhile, the essential nutrients calcium, sodium, iron, potassium, copper and magnesium are found in adequate quantities [21]. In addition, a special class of compounds called the annonaceous acetogenins are reported to be present in majority. Annonaceous acetogenins are called so due to their unique presence in only the plants belonging to *Annonaceae* family, are rendered responsible for the significant biological activities of the plant. Also the *A. muricata* alkaloids and phenolics are believed value additions with regard to the medicinal significance [11].

Chemistry of Acetogenins

As mentioned earlier, the Acetogenins are a class of phytochemicals unique to the family *Annonaceae.* These compounds which are usually 35 to 37 carbons long are found to be the metabolically derived, via the polyketide pathway, from fatty acid molecules that are 32 to 34 carbons in length [11,22]. The same has been demonstrated using a combination of fatty acids at the C2 of a 2-propanol unit, which results in a methyl-substituted α, β-unsaturated, γ-lactone [12,23]. Notwithstanding, Annonaceous Acetogenins are a set of polyether compounds which can be perceived to be a group of least-investigated phytocompounds [11]. From what is known so far, the acetogenins are constituted by a 32 to 34 carbons long aliphatic chain with its terminus attached to a butanolide or lactone. In addition, reports suggest that tetrahydrofuran, tetrahydropyran, ketone, hydroxyl or epoxide side-chains may be featured in these bioactive compounds [24-27]. So far, as many as 500 acetogenins have been reported to be found in the plants belonging to the *Annonaceae* family, of which nearly 120 acetogenins have been identified in the *A. muricata* alone [12,13,28].



n=1-3, R, R'=hydrocarbon chain having oxygenated moieties and/or double bonds

Figure 3: Representative Structure of Annonaceous Acetogenins (***Source:*** *Kojima and Tanaka (2009)*).

Reported Anti-Breast Cancer Activity of *A. Muricata* Acetogenins

Acetogenins have been reported to impose the ataxia telangiectasia mutated (ATM) signalling pathway related checkpoint kinase 2 (CHK2) downregulation leading to the enhancement of the chemo- and radio-sensitizing effects in cancer therapy [29]. Yiallouris, et al. [30] concluded using an *in silico* prediction method that the acetogenin Annonacin promoted selective cytotoxicity, in cancer cells, mediated by the sodium/potassium (NKA) – as well as the sarcoplasmic reticulum (SERCA) ATPase pump – dependent pathways [30]. In another study, the acetogenins annomuricin A, annomuricin B, annomuricin C, annomuricin E, annomutacin, murihexocin A, murihexocin B, and murihexocin C were evaluated for their *in silico* anticancer potential in comparison with gefitinib, an EGFR inhibitor used in cancer therapeutics. The acetogenins were found to have lowest hypoxia-inducible factor-1alpha (HIF-1α) binding energies of -6.1, -7.2, -7.1, -7.3, -6.9, -7.9, -6.7, -7.6, and -7.9 kcal/mol, respectively, while gefitinib showed the lowest binding energy of -6.7 kcal/mol. Indicating that the evaluated acetogenin molecules were potent anticancer agents [31]. Notwithstanding, no *in silico* study has been conducted to validate the cytotoxic potential of acetogenins identifed with specific anti-breast cancer activity.

Out of above reported *A. muricata* acetogenins, only 10 have been identified as potent anti-breast cancer agents and they are: (I) annomuricin A, (II) annomuricin B, (III) annomuricin C, (IV) muricatocin C, (V) muricatacin, (VI) *cis*-annonacin, (VII) *cis*-annonacin-10-one, (VIII) *cis*-goniothalamicin, (IX) arianacin, and (X) javoricin [12].

Annomuricins A and B

Wu, et al. [32] reported the anti-cancer activity of the monotetrahydrofuran containing *A. muricata* acetogenins, annomuricin A and annomuricin B (Figures 4&5) [33]. While annomuricin A has been reported to be present in the leaves and pericarp of *A. muricata* plant, annomuricin B is found only in its leaves [17,33]. Both the compounds were found to comprise of five hydroxyl groups, with two hydroxyl groups being vicinal. The *A. muricata* extracts, fractions, isolates and derivatives were subjected to a seven-day cytotoxicity assay against the human solid tumor cell lines, for lung carcinoma (A549), breast carcinoma (MCF-7), and colon adenocarcinoma (HT-29), to determine their potent cytotoxic behaviours. The results indicated that the compounds annomuricins A and B, as well as their acetonide derivatives demonstrated potent anticancer activity which was on par with the Adriamycin positive control. The ED_{50} concentrations of annomuricin A, annomuricin B, acetonide derivative of annomuricin A, acetonide derivative of Annomuricin B, and Adriamycin were reported to be >1.0, >1.0, $2.78x10^{-4}$, $1.41x10^{-4}$, and $1.26x10^{-1}$, respectively [33].

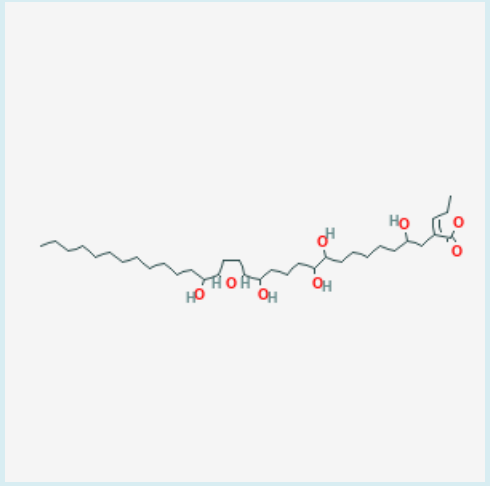


Figure 4: Chemical Structure of Annomuricin A (***Source:*** *PubChem*).

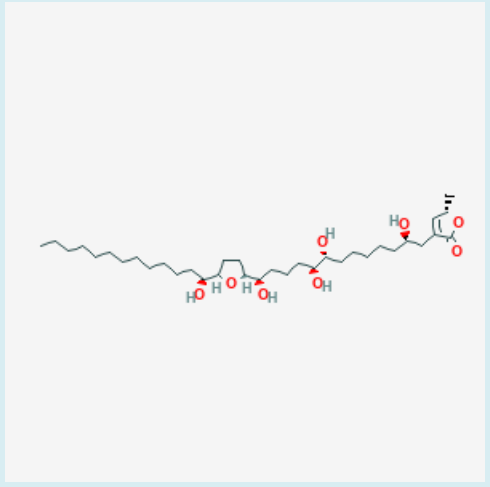


Figure 5: Chemical Structure of Annomuricin B (***Source:*** *PubChem*).

Annomuricin C and Muricatocin C

The annomuricin C and muricatocin C monotetrahydrofuran acetogenins (Figures 6&7) were reportedly found exclusive to the *A. muricata* leaves by Wu, et al. [32,33]. These compounds possessing five hydroxyl groups, were found to have two hydroxyl groups at the C10/C11 and C10/C12 positions, respectively. Both the acetogenins were found to exhibit cytotoxicity against the human solid tumor cell lines A-549 for lung cancer and MCF-7 for human breast cancer. Additionally, the cytotoxicity of either was found to be enhanced significantly upon acetonide derivation, similar to what was observed in the case of the annomuricins A and B [32].

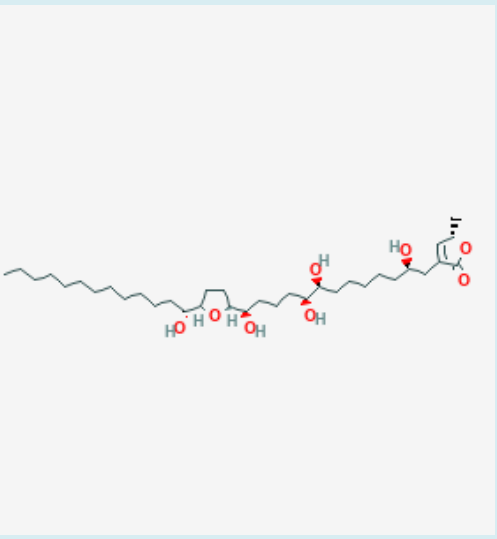


Figure 6: Chemical Structure of Annomuricin C (***Source:*** *PubChem*).

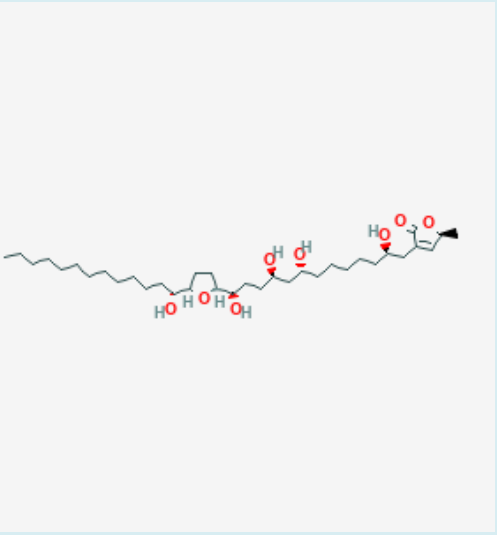


Figure 7: Chemical Structure of Muricatocin C (***Source:*** *PubChem*).

Muricatacin

Muricatacin (Figure 8) is a biologically active constituent unique to the *A. muricata* seeds. The compound is very well known for its obvious structural similarities to annonacin, a neurotoxic acetogenin found in the leaves, seeds and pericarp of the plant. Muricatacin has been reported to exhibit potent antiproliferative behavior against the breast cancer MCF-7 cell lines, apart from those of lung and colorectal cancers [34].

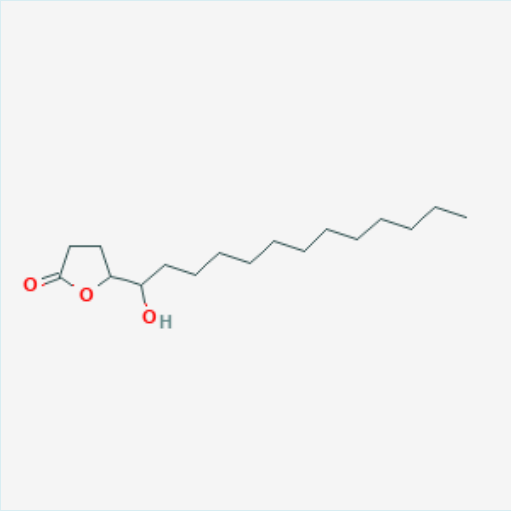


Figure 8: Chemical Structure of Muricatacin (***Source:*** *PubChem*).

cis-Annonacin, *cis*-Annonacin-10-one, *cis*-Goniothalamicin, Arianacin and Javoricin

The above five acetogenins (Figures 9-13), *cis*-Annonacin, *cis*-Annonacin-10-one, *cis*-Goniothalamicin, Arianacin, and Javoricin, were exclusively found in the seed of *A. muricata* plant [35]. While the first three were among the first-of-kind acetogenins reported with *cis-monotetrahydrofuran* ring, the other two were found to be composed of a regular tetrahydrofuran moiety. All the molecules in their pure form demonstrated relative potencies against the breast, lung and colon cancer cell lines. In fact, the *cis*-Annonacin molecule reportedly exhibited a cytotoxic potential 10,000 times that of the Adriamycin positive control [35,36].

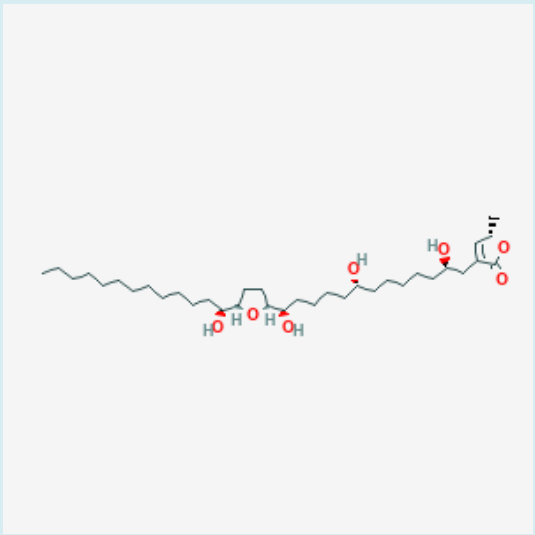


Figure 9: Chemical Structure of *cis*-Annonacin (***Source:*** *PubChem*).

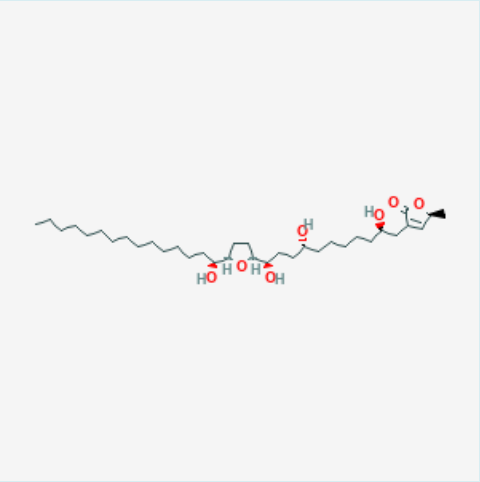


Figure 10: Chemical Structure of *cis*-Annonacin-10-one (***Source:*** *PubChem*).

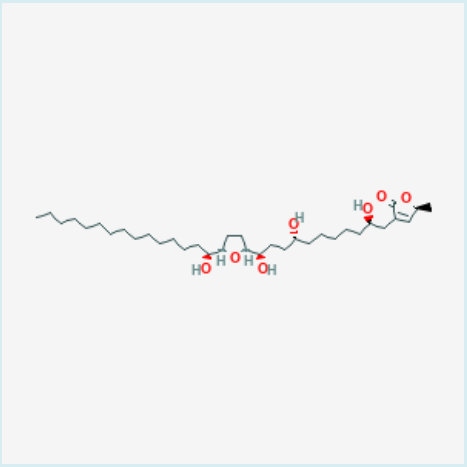


Figure 11: Chemical Structure of cis-Goniothalamicin (Source: PubChem)

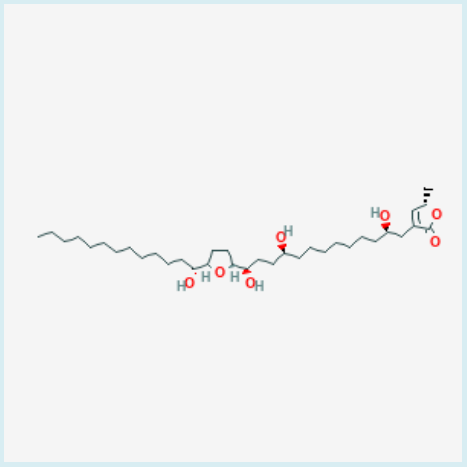


Figure 12: Chemical Structure of Arianacin (Source: PubChem).

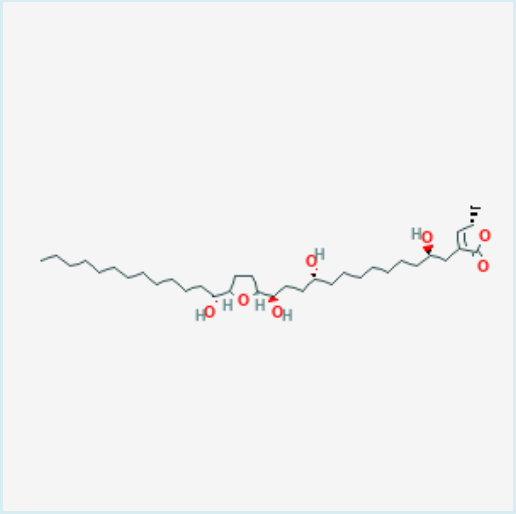


Figure 13: Chemical Structure of Javoricin (Source: PubChem).

Conclusion

In conclusion, the above studies indicate the presence of chemically unique compounds, Acetogenins, in the *A. muricata* species, and these compounds are found to contribute towards the biomedical significance of the plant. Notwithstanding, the available knowledge in this context is preliminary, highlighting the need for mechanistic evaluation clubbed with *in vivo* as well as *in silico* validation of the observed cytotoxicity, apart from understanding the tumor-specific selectivity/localized effect of the above said cytotoxicity. Thereby implying that the *A. muricata* acetogenins may be of a great medicinal value if studied explicitly, enabling new dimensions in to cancer therapeutics.

Conflicts of Interest

No conflicts of interests exist.

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