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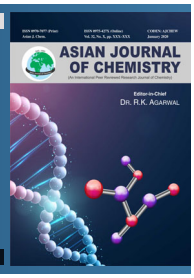

REVIEW

Annonaine an Alkaloid from the Leaves of Custard Apple (*Annona squamosa*): A Comprehensive Review on its Phytochemicals and Pharmacological Activities

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Annona squamosa is most widely distributed in tropical and subtropical region native to tropical America comes under the Annonaceae family. It is a widely used tree having edible fruits called as custard apple which is eatable. *Annona squamosa* plant also contains 35-42 mg/100 g of vitamin C and significant value of nutrient like thiamine, amino acid, riboflavin, niacin, calcium, potassium and dietary fibers. It also contains the phytoconstituents like diterpenes, alkaloids, cyclopeptides and annonaceous acetogenins proved by phytochemistry investigations. The plant *Annona squamosa* show a number of pharmacological activities like insecticidal, anticancer, hypoglycemic, antioxidant, antimalarial, analgesic and wound healing activity. The vermicidal effect of leaves is responsible for the treatment of tumors, wounds and other skin infections. A number of alkaloids were isolated from the leaves of plant. Most of them belong to aporphine group of alkaloids. Among all the phytoconstituents an alkaloid Annonaine, plays a vital role for its biological activity. The present review represents the phytochemical constituents, biological action, traditional as well as medicinal uses of *Annona squamosa.* Sugar apple might be the better explored plant part used in treatment of many disorders and the present critical study will hopefully provide a disease free and healthy life to the human society.

Keywords: *Annona squamosa*, Traditional medicine, Phytochemicals, Alkaloid annonaine, Pharmacological activity.

INTRODUCTION

Plants are the rich source of bioactive materials which play a vital role in various human disorder condition as well as in agricultural field and also they remarkably enhance the bio-activities of other substances [1]. Most of the unknown species belongs to the plant kingdom having the phytoconstituents of the therapeutic and nutritional value have yet to be proved. Fruits and vegetables are the repository house for a list of nutritional compounds. The extraction of phytoconstituents from plants and the initiation of drug formulation is a sophisticated technology [2].

Annona squamosa Linn. belongs to the family Annonaceae, a species of Annona native to tropical America. The trees are 10-12 ft. high with the leaves aligned alternately on short hairy petiole having irregular branches. The whole plant *i.e.* the leaves, fruits, root and bark show a high range of medicinal as well as nutritional value as they contain vitamin C and significant value of nutrient like thiamine, amino acid, riboflavin, calcium, potassium and dietary fibers. The plant is particularly available in northern South America basically in Columbia, Ecuador and Peru. In the year 1971, it was first cultivated in the Andeas and was first plan California [3]. Since last 500 years, India acts as the secondary centre of diversity of *Annona squamosa* plant carrying very large and good commercial importance. The fruit of *Annona squamosa* plant commonly called custard apple, sharifa or sitaphal, covered by a scaly skin having a diameter of 6-10 cm.

It is widely distributed in the tropical and eastern part of India. It is an earth bound woody perennial tree with deciduous leaves having characteristic odour. The leaves are brilliant green in the upper part and bluish green below, ovate to lanceolate shape having petioles 0.7-1.5 cm and lamina about 10 cm × 5 cm alternately arranged in a zigzag manner. Annonaine, an alkaloid plays a vital role to exhibit a number of biological activities isolated from the bark and leaves of *Annona squamosa*

plant [4]. The leaf extract of *Annona squamosa* was reported to possess hypoglycemic and antidiabetic effect [4,5]. The different phytoconstituents isolated from leaves like flavonoids [6], aporphine alkaloids [7] and glycosides [8] were reported. *Annona squamosa* (genus: *Annona* L.) is a widely available plant carrying 130 genus and 2300 species [9,10].

Flowers of *Annona squamosa* is 2-2.5 cm with three green sepals and six petals. The flowers have spirally arranged stamens with numerous united carpels. The fruit contains hard black seed covered with fruit pulp (Fig. 1), which is sweet and white to light yellow divided into 20-38 segments each and also some trees produce seedless fruit. The fruits are rich in iron, calcium and phosphorus [11].

Basically flowering plants with trees, shrubs, *etc*. come from custard apple family or Annonaceae family [12,13] where Annona means yearly produce emerged from the Latin word 'anon' native in the tropical region, less number of species are found in temperate region. Out of 2300 total species 900 species belong to neotropical, 450 belong to afrotropical and other species belong to Indo-Malaya [14]. Annonanceae family have 130 genera, out of that most widely spread genera are *Annona*, *Annonidium*, *Rolliania*, *Melodorum*, *Stelechocarpus* and *Asimina*. Also, *Atemoya* a relative of both *Annona cherimola* and *Annona squamosa* found mostly in tropical America [9,15]. The biological activity of *Annona squamosa* act as an interlink between food and pharmaceutical potential for the commercial use [16]. The objective of the present review is to evaluate the phytochemical characteristic of *Annona squamosa* leaf along with the screening of their physico-chemical nature and also the major phytoconstituents that contribute to various biological activities.

Classification

Annona squamosa L. plant can be classified according to their kingdom, class, division, genus and species [17].

Kingdom: Plantae; Subkingdom: Tracheobionta; Division: Magnoliophyta; Class: Magnoliopsida; Family: Annonaceae Genus: Annona L.; Species: *Annona squamosa*.

Therapeutic use: The plant *Annona squamosa* is associated with the therapeutic use that includes antifertility and anti-tumor activities observed in mice and rats. The people of few states of India extensively used the young leaves of *Annona squamosa* due to its antidiabetic activity. They were consuming a combination of black pepper along with 4 to 5 newly fertile leaves in the early morning and for the evidence they got 80% of the positive result for the treatment of diabetes. The aqueous leaf extract of *Annona squamosa* was also used against hyperthyroidism, causative factor for diabetes mellitus [18].

The seed extract was investigated to possess post-cortical anti-fertility activity. The extract of seeds, fruits showed activity against various insects and also used as an irritant of conjunctiva. In the acute dysentery and as a drastic purgative the root extract was widely used [19,20]. In Yunani medicine, it is reported that the extract of seed of the plant is used as aborient, to eliminate lice in hair and also the combination of gram flour

Fig. 1. (A) Whole plant of *A. squamosa*, (B) Fruit pulp, (C) Leaves, (D) Seeds [Ref. 19]

and the oil and resin produced from seed are used for hair washing [17].

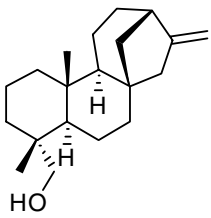
The fruits of *Annona squamosa* are highly nutritious and also have hypoglycemic activity which showed positive effect in the experimental animals [21]. It was reported that srikayas can increase the muscle strength and have the capacity to enrich blood [22]. *Annona squamosa* was used for the contraction of skin cells and other body tissues, in the management of diarrhea and also used as insecticide [23]. It was reported that in the tropical area the Parkinsonism can be treated by the consumption of Annonaceous edible species by inhibiting the ATP production during the electron transport chain in mitochondria specially in the site of respiratory complex-I [24,25].

Phytochemicals: The sweetness of custard apple is due to the presence of 28% sugar in which sucrose content is 2.53%, dextrose 5.05% and laevulose 0.04% with aromatic flavours. Although the sugar content is high but its glycemic index is low and hence shows moderate glycemic load. The components like vitamin C, iron, calcium, thiamine, amino acid, potassium, carotene, riboflavin, niacin, ascorbic acid, magnesium and dietary fibers are present in significant quantities. The specific extracted chemicals from the plants are aliphatic ketones (palmitone), organic acids (hexanoic acid and octanoic acid) and purines *etc*. About 59 compounds were isolated from leaf oil by GC-MS analysis [26]. The active components were β- caryophyllene (31.4%), δ- candinene (6.7%), α-candinol (4.3%) and isoquinoline alkaloid. Apart from that other alkaloids are it also contain annonaine, aporphine, coryeline, isocorydine and glaucine,samoquacine, aporphine, benzylisoquinoline, protoberberine and tetrahydroisoquinolinefrom leave extract [27].

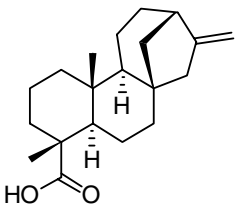
The bark of *Annona squamosa* was extracted from unsaponified petroleum ether and an active agent caryophyllene oxide was isolated which show promising biological activities [28]. A series of phytochemicals and phytoconstituents were reported by the extensive phytochemical evaluation of different portions of *Annona squamosa* plant including diterpenes, alkaloids, annonaceousacetogenins, cyclopeptides and essential oils.

Diterpenes: There are 34 diterpenes extensively found in barks of *Annona squamosa*, active in ovarian and lung cancer as antitumor substances and majority of them (Fig. 2) have chemical composition of ent-kauranediterpenes [29].

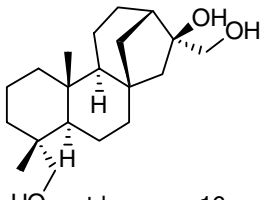
Alkaloids: Antispasmodic, bronchodilatory, antihypertensive and anti-histaminic activities of near about 19 alkaloids (Fig. 3) were reported those were extracted and isolated from the stems and leaves of *Annona squamosa* plant [30]. Among all these alkaloids anonaine (structure 27) is a bioactive benzylisoquinoline alkaloid belongs to family Annonaceae first extracted from the plant *Annona reticulata* [31], which show an effect on the central nervous system [32] and a wide range of biological activities like anticancer, vasorelaxation, antioxidant, antiparasitic and antimicrobial activities. Anonaine shows its activity by different mechanisms like generating nitricoxide and reactive oxygen species, reducing intracellular glutathione concentration, activating caspases and apoptosis-related proteins and damage to DNA and hence inhibits the growth in human



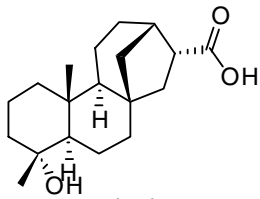
ent-kaur-16-en-19-ol
[Ref. 42]



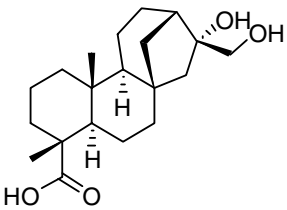
ent-kaur-16-en-19-oic acid
[Ref. 42,43]



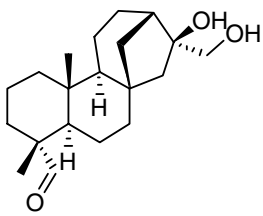
ent-kaurane-16, 17, 19-triol
[Ref. 42]



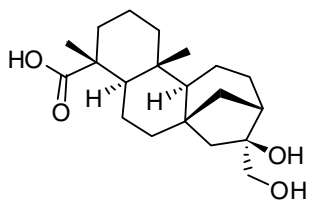
4-hydroxy-19-nor-ent-kauran-17-oic-acid
[Ref. 42]



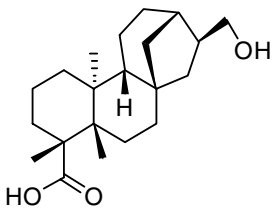
16 α,17-dihydroxy-ent-kauran-19-oic acid
[Ref. 42,44]



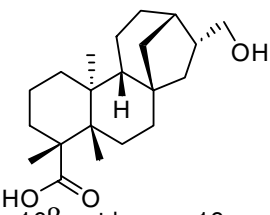
ent-16,17-dihydroxykauran-19-al
[Ref. 42,44]



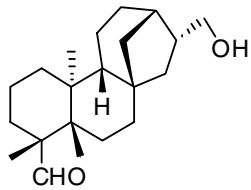
16 β,17-dihydroxy-ent-kauran-19-oic acid
[Ref. 42,45]



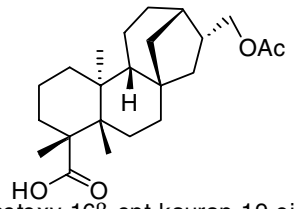
17-hydroxy-16α-ent-kauran-19-oic acid
[Ref. 42,46]



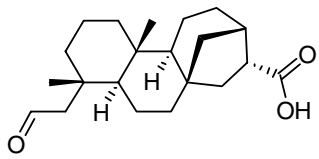
17-hydroxy-16β-ent-kauran-19-oic acid [Ref. 42,46]



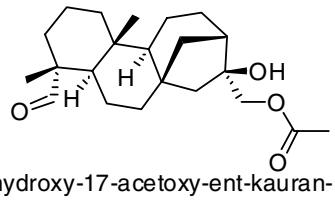
17-hydroxy-16β-ent-kauran-19-al [Ref. 42,46]



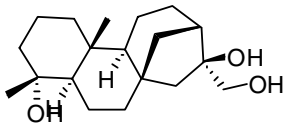
17-acetoxy-16β-ent-kauran-19-oic acid
[Ref. 42]



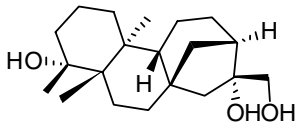
19-formyl-ent-kauran-17-oic acid
[Ref. 42]



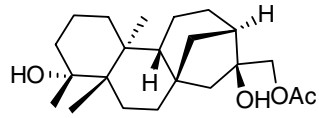
16β-hydroxy-17-acetoxy-ent-kauran-19-al
[Ref. 42,49]



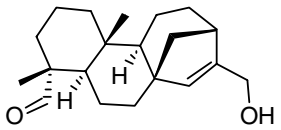
19-nor-ent-kaurane-4,16,17-triol
[Ref. 29,42]



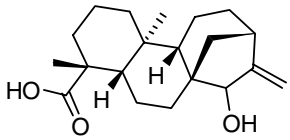
(4α-)19-nor-ent-kaurane-4,16,17-triol)
[Ref. 43]



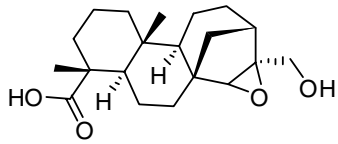
(4α,16α)-17-(acetyloxy)-19-nor-ent-kaurane-4,16-diol [Ref. 43]



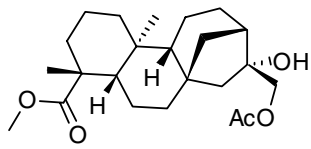
17-hydroxy-ent-kaur-15-en-19-al
[Ref. 43]



ent-15β-hydroxy-kaur-16-en-19-oic acid
[Ref. 29]

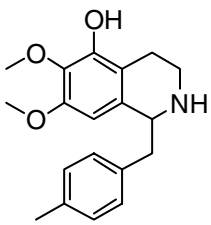


15,16-epoxy-17-hydroxy-ent-kauran-19-oic acid
[Ref. 29]

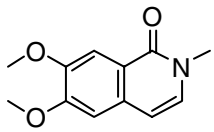


16,17-dihydroxy-ent-kauran-19-oic acid methyl ester
[Ref. 29,43]

Fig. 2. Structure of diterpenes of bark of *A. squamosa*



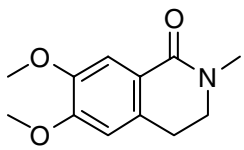
anomuricine
[Ref. 47]



N-methyl-6,7-dimethoxyisoquinolone

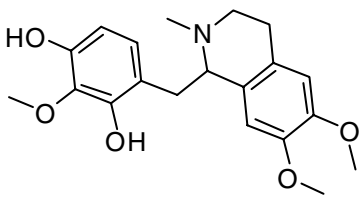
This name appears to be ambiguous

[Ref. 47,48]

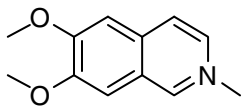


6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1-one

[Ref. 47]

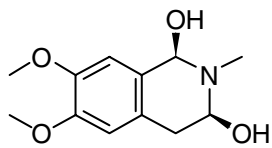


((6,7-dimethoxy-2-methyl-1,2,3,4-tetra-hydroisoquinolin-1-yl) methyl)-2-meth-oxybenzene-1,3-diol
[Ref. 49]



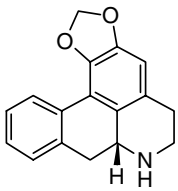
6,7-dimethoxy-2-methylisoquinol

[Ref. 49]



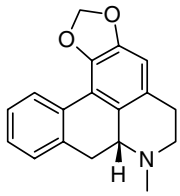
(1R,3S)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1,3-diol

[Ref. 49]



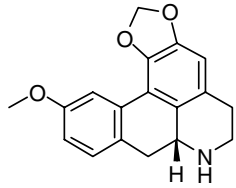
(12R)-3,5-dioxa-11-azapentacyclo [10.7.1.02,6.08,20.014,19] icosa-1(20),2(6),7,14,16,18-hexaene

[Ref. 7]



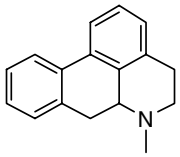
(12R)-11-methyl-3,5-dioxa-11-azapentacyclo [10.7.1.02,6.08,20.014,19] icosa-1(20),2(6),7,14,16,18-hexaene

[Ref. 50]



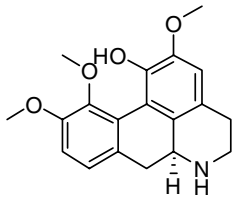
(12R)-17-methoxy-3,5-dioxa-11-azapentacyclo[10.7.1.02,6.08,20.014,19] icosa-1(20),2(6),7,14(19),15,17-hexaene

[Ref. 7]



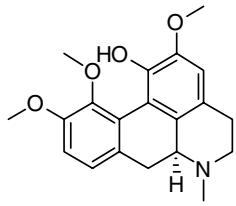
6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline

[Ref. 7]



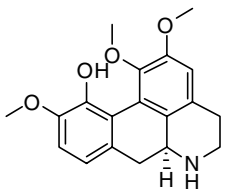
(6aS)-2,10,11-trimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-1-ol

[Ref. 7]



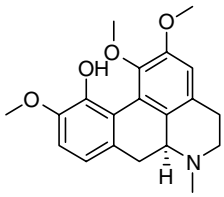
(6aS)-2,10,11-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-1-ol

[Ref. 7]



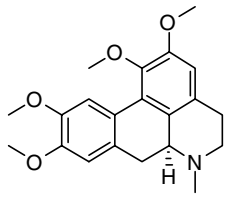
(6aS)-1,2,10-trimethoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-11-ol

[Ref. 7]



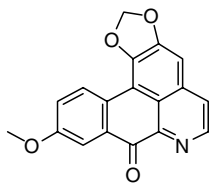
(6aS)-1,2,10-trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-11-ol

[Ref. 7]



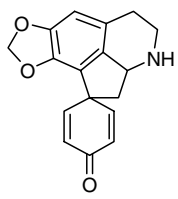
(6aS)-1,2,9,10-tetramethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline

[Ref. 7]



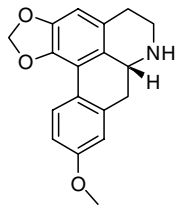
16-methoxy-3,5-dioxa-11-azapentacyclo [10.7.1.02,6.08,20.014,19]icosa-1(20), 2(6),7,9,11,14(19),15,17-octaen-13-one

[Ref. 48]



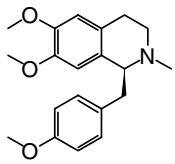
2a',3',4',5'-tetrahydro-2'*H*-spiro[cyclohexane-1,1'-cyclopenta[*ij*][1,3]dioxolo[4,5-*g*] isoquinoline]-2,5-dien-4-one

[Ref. 7]



(*R*)-10-methoxy-6,7,7a,8-tetrahydro-5*H*-[1,3]dioxolo [4',5':4,5]benzo[1,2,3-*de*]benzo[*g*]quinoline

[Ref. 51]



(*S*)-6,7-dimethoxy-1-(4-methoxybenzyl) -2-methyl-1,2,3,4-tetrahydroisoquinoline

[Ref. 48]

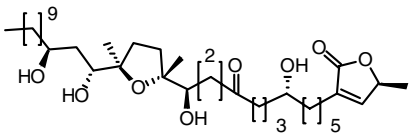
Fig. 3. Structure of alkaloids of stems and leaves of *A. squamosa*

lung carcinoma H1299 cells *in vitro* [33] human cervical cancer [34].

***Annonaceous acetogenins*:** A series of natural products were constituted by isolation of acetogenins exclusively from Annonaceous species and were widely distributed throughout the tropical and subtropical area of the world [35,36]. Acetogenin groups of compounds are the plant products consist of 35-37 C-atoms and are originated from unbranched 32-34 carbon

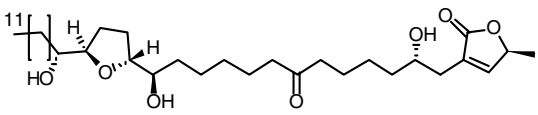
fatty acids. Most of the acetogenins consist of long fatty chain like 4-deoxyannoreticuin, *cis*-4 deoxyannoreticuin with α,β-unsaturation [37]. In 1982, acetogenin was originated from *Uvaria accuminata*, but from different parts of the species of Annonaceae family more than 500 acetogenins (Fig. 4) have been discovered [38]. Due to the particular and well-defined structures and distinctive bioactivities acetogenins have shown extensive scientific interest. Acetogenins provide different biological activities against various insects, parasites and fungi [39,40].

Cyclic peptides: The cyclic peptides are included under the protein group of compounds (cyclotide family) is adequately belong to Rubiaceae family. The compounds cyclic peptides isolated from the plant *Annona squamosa* under this family contain a unique amide head to tail cyclized peptide, which is incorporated as cystine knot along with two disulfide



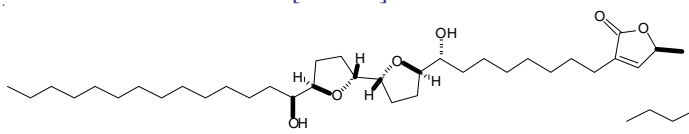
(*S*)-3-((2*R*,6*R*)-6-((2*R*,5*R*)-5-((1*R*,3*S*)-1,3-dihydroxypentyl)-2,5-dimethyltetrahydrofuran-2-yl)-2,6-dihydroxy-4-oxohexyl)-5-methylfuran-2(5*H*)-one

[Ref. 52]



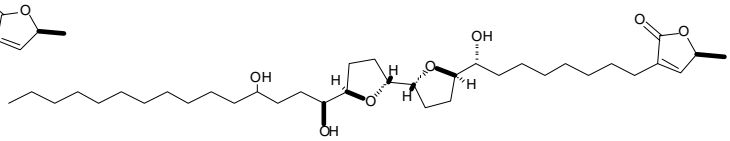
(*S*)-3-((2*S*,13*R*)-2,13-dihydroxy-13-((2*R*,5*R*)-5-((*R*)-1-hydroxypropyl)tetrahydrofuran-2-yl)-7-oxotridecyl)-5-methylfuran-2(5*H*)-one

[Ref. 53]



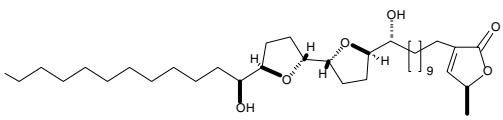
(2*S*)-4-[(8*R*)-8-[(2*R*,5*R*)-5-[(2*R*,5*R*)-5-[(1*S*)-1,5-dihydroxyhexadecyl]oxolan-2-yl]oxolan-2-yl]-8-hydroxyoctyl]-2-methyl-2*H*-furan-5-one

[Ref. 54,55]



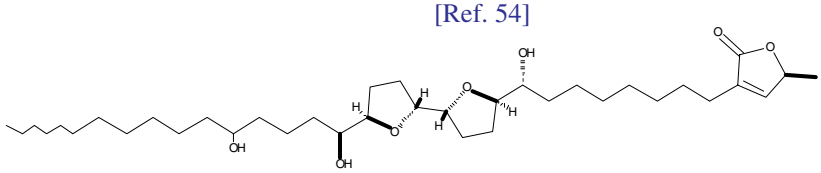
(5*S*)-3-((8*R*)-8-((2*R*,2′*R*,5*R*,5′*R*)-5′-((1*S*)-1,4-dihydroxyhexadecyl)octahydro-[2,2′-bifuran]-5-yl)-8-hydroxyoctyl)-5-methylfuran-2(5*H*)-one

[Ref. 54]



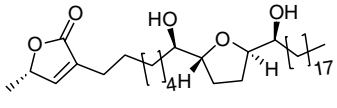
(*S*)-3-((*R*)-8-hydroxy-8-((2*R*,2′*R*,5*R*,5′*R*)-5′-((*S*)-1-hydroxyundecyl)-5-methyloctahydro-[2,2′-bifuran]-5-yl)octyl)-5-methylfuran-2(5*H*)-one

[Ref. 54,55]



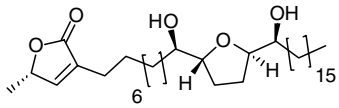
(5*S*)-3-((8*R*)-8-((2*R*,2′*R*,5*R*,5′*R*)-5′-((1*S*)-1,5-dihydroxypentadecyl)octahydro-[2,2′-bifuran]-5-yl)-8-hydroxyoctyl)-5-methylfuran-2(5*H*)-one

[Ref. 56]



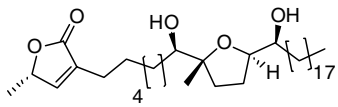
(*S*)-3-((*R*)-4-hydroxy-4-((2*R*,5*R*)-5-((*S*)-1-hydroxypropyl)tetrahydrofuran-2-yl)butyl)-5-methylfuran-2(5*H*)-one

[Ref. 54,55]



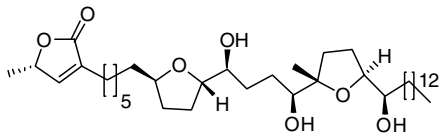
(*S*)-3-((*R*)-4-hydroxy-4-((2*R*,5*R*)-5-((*S*)-1-hydroxypropyl)tetrahydrofuran-2-yl)butyl)-5-methylfuran-2(5*H*)-one

[Ref. 54,55,57]



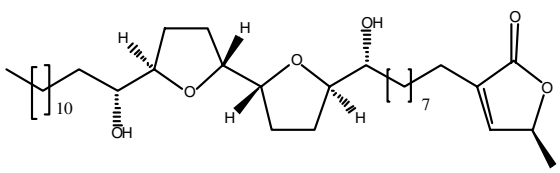
(*S*)-3-((*R*)-4-hydroxy-4-((1*S*,3*S*)-3-((*S*)-1-hydroxypropyl)cyclopentyl)butyl)-5-methylfuran-2(5*H*)-one

[Ref. 54]



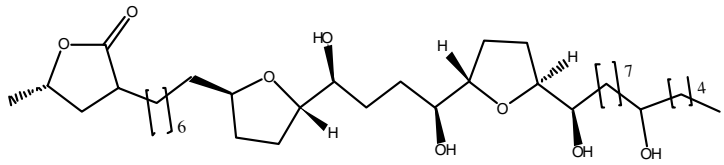
(*S*)-3-(2-((2*R*,5*S*)-5-((1*S*,4*S*)-1,4-dihydroxy-4-((2*S*,5*S*)-5-((*R*)-1-hydroxypropyl)-2-methyltetrahydrofuran-2-yl)butyl)tetrahydrofuran-2-yl)ethyl)-5-methylfuran-2(5*H*)-one

[Ref. 54]



(*S*)-3-((*R*)-3-hydroxy-3-((2*R*,2′*R*,5*R*,5′*R*)-5′-((*R*)-1-hydroxybutyl)octahydro-[2,2′-bifuran]-5-yl)propyl)-5-methylfuran-2(5*H*)-one

[Ref. 54]



(5*S*)-3-(2-((2*R*,5*S*)-5-((1*S*,4*S*)-4-((2*S*,5*S*)-5-((1*R*)-1,3-dihydroxypentyl)tetrahydrofuran-2-yl)-1,4-dihydroxybutyl)tetrahydrofuran-2-yl)ethyl)-5-methyldihydrofuran-2(3*H*)-one

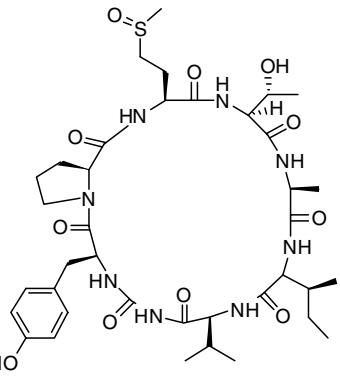
[Ref. 55,57]

Fig. 4. Structure of annonaceous acetogenins of different parts of *A. squamosa*

bonds (Fig. 5). The combined structure of cyclic cystine knot forms the most complex, chemically stable and bioactive substances [41], which are responsible for showing the activities against various insects, anticancer, hypoglycemic, antioxidant and antilipidemic activity [17].

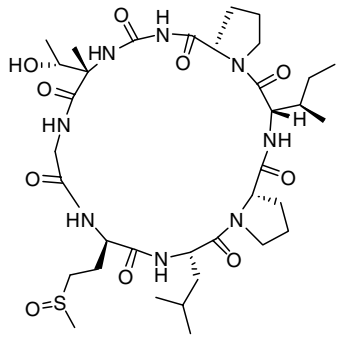
Essential oils: The GC-MS analysis proves that in plant *Annona squamosa* the leaf oil contains sesquiterpenes along with β-caryophyllene and germacrene D which are collected from North Indian planes [61]. Apart from that the leaf oil of *Annona squamosa* also contains the compounds like 27.4% of (*E*)-caryophyllene, 17.1% of germacrene D and (10.8%) of bicyclogermacrene collected from Brazil [62]. It was also identified from other investigation that *Annona squamosa* bark oil contains adequate amount of volatile oil consisting of (29.38%) of caryophyllene oxide, (19.13%) of kaur-16-ene, (11.44%) of germacrene D, (4.48%) of bisabolene and (3.46%) of 1*H*-cycloprop(e)-azulene [63]. The monoterpenes like sabinene, limonene and pinene were found in fruit pulp of *Annona squamosa* in high concentration [64].

Phytoconstituents *viz*. alkaloids, cyclic peptides, acetogenins and ent-kuranedi-terpenoids, isolated from different part of plant *Annona squamosa* Linn. are listed in Table-1. While a



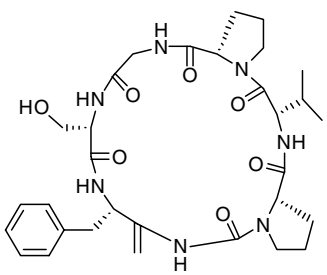
(3*S*,6*S*,9*S*,20*S*,25a*S*)-12-((*S*)-*sec*-butyl)-20-(4-hydroxybenzyl)-6-((*R*)-1-hydroxyethyl)-15-isopropyl-9-methyl-3-(2-(methylsulfinyl)ethyl)hexadecahydro-1*H*-pyrrolo[1,2-*f*][1,3,6,9,12,15,18,21]octaazacyclotricosin-1,4,7,10,13,16,18,21(17*H*)-octaone

[Ref. 58]



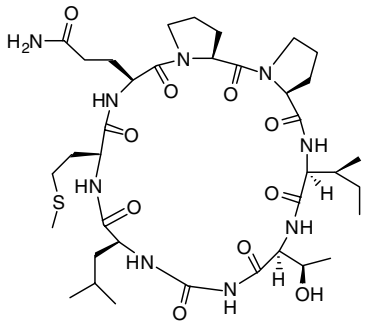
(6*S*,9*R*,15*S*,25*S*,27a*S*)-25-((*R*)-*sec*-butyl)-15-((*R*)-1-hydroxyethyl)-6-isobutyl-15-methyl-9-(2-(methylsulfinyl)ethyl)octadecahydro-5*H*-dipyrrolo[2,1-*e*:2',1'-*k*][1,3,6,9,12,15,18,21]octaazacyclotricosin-5,8,11,14,17,19,24,27(18*H*)-octaone

[Ref. 59]



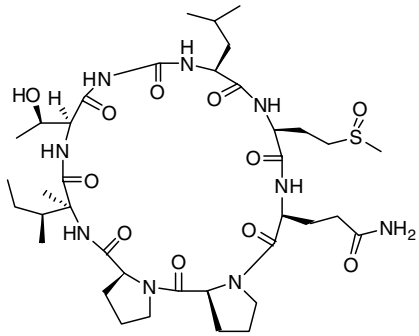
(8*S*,11*S*,16a*S*,22*S*,24a*S*)-8-benzyl-11-(hydroxymethyl)-22-isopropyl-7-methyleneoctadecahydrodipyrrolo[1,2-*c*:1',2'-*i*][1,3,6,9,12,15,18]heptaazacycloicosine-5,10,13,16,21,24-hexaone

[Ref. 60]



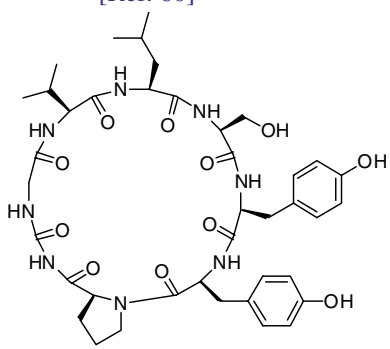
3-((6*S*,12*S*,17*S*,20*S*,22a*S*,27a*S*)-20-((*S*)-*sec*-butyl)-17-((*R*)-1-hydroxyethyl)-12-isobutyl-9-(2-(methylthio)ethyl)-5,8,11,14,16,19,22,27-octaoxohexacosahydro-1*H*-dipyrrolo[2,1-*k*:2',1'-*n*][1,3,6,9,12,15,18,21]octaazacyclotricosin-6-yl)propanamide

[Ref. 60]



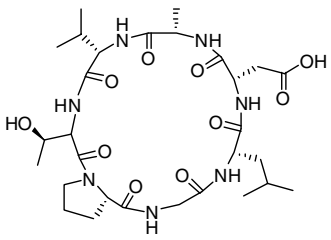
3-((6*S*,9*S*,12*S*,17*S*,20*S*,22a*S*,27a*S*)-20-((*S*)-*sec*-butyl)-17-((*R*)-1-hydroxyethyl)-12-isobutyl-20-methyl-9-(2-(methylsulfinyl)ethyl)-5,8,11,14,16,19,22,27-octaoxohexacosahydro-1*H*-dipyrrolo[2,1-*k*:2',1'-*n*][1,3,6,9,12,15,18,21]octaazacyclotricosin-6-yl)propanamide

[Ref. 60,68]



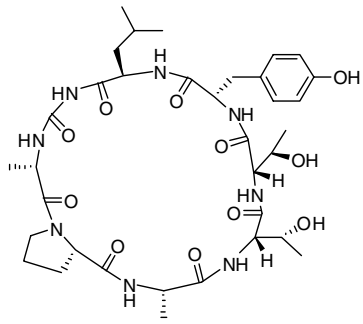
(8*S*,11*S*,14*S*,17*S*,20*S*,25a*S*)-17,20-bis(4-hydroxybenzyl)-14-(hydroxymethyl)-11-isobutyl-8-isopropylhexadecahydro-1*H*-pyrrolo[2,1-*e*][1,3,6,9,12,15,18,21]octaazacyclotricosin-1,3,6,9,12,15,18,21(2*H*)-octaone

[Ref. 59,60]



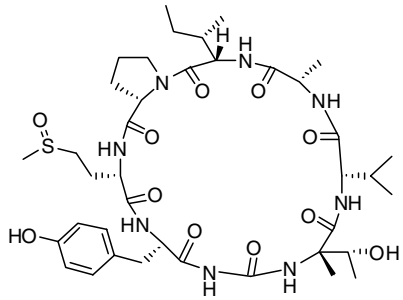
2-((6*S*,9*S*,12*S*,15*S*,23a*S*)-18-((*R*)-1-hydroxyethyl)-6-isobutyl-15-isopropyl-12-methyl-1,4,7,10,13,16,19-heptaoxodocosahydro-1*H*-pyrrolo[1,2-*a*][1,4,7,10,13,16,19]heptaazacyclohenicosin-9-yl)acetic acid

[Ref. 59]



(3*S*,6*S*,9*S*,15*R*,20*S*,25a*S*)-12-(4-hydroxybenzyl)-6,9-bis((*R*)-1-hydroxyethyl)-15-isobutyl-3,20-dimethylhexadecahydro-1*H*-pyrrolo[1,2-*f*][1,3,6,9,12,15,18,21]octaazacyclotricosin-1,4,7,10,13,16,18,21(17*H*)-octaone

[Ref. 59]



(3*S*,11*S*,17*S*,20*S*,25a*S*)-20-((*S*)-*sec*-butyl)-6-(4-hydroxybenzyl)-11-((*R*)-1-hydroxyethyl)-14-isopropyl-11,17-dimethyl-3-(2-(methylsulfinyl)ethyl)hexadecahydro-1*H*-pyrrolo[2,1-*k*][1,3,6,9,12,15,18,21]octaazacyclotricosin-1,4,7,9,12,15,18,21(8*H*)-octaone

[Ref. 59]

Fig. 5. Structure of cyclic peptides of plant *A. squamosa*

TABLE-1
PHYTOCONSTITUENTS ISOLATED FROM DIFFERENT PART OF PLANT *Annona squamosa* Linn.

S. No.	Plant's parts	Isolated constituents	Ref.	S. No.	Plant's parts	Isolated constituents	Ref.
1	Leaves, tender stem, bark, roots, seeds	Anonaine	[65]	33	Stem, Bark	Bullatacin	[76]
2	Roots	Anolobine	[65]	34	Stem, Bark	Bullatacinone	[76]
3	Leaves, tender stem	Aporphine	[65]	35	Bark	4-Deoxyannoreticuin	[77]
4	Leaves, tender stem, bark	Corydine	[65]	36	Bark	*cis*-4-Deoxyannoreticuin	[77]
5	Leaves, tender stem, bark, roots	Isocorydine	[65]	37	Bark	2,4-*cis*-Squamoxinone	[77]
6	Leaves, tender stem	Norcorydine	[65]	38	Bark	2,4-*cis*-Mosinone A	[78]
7	Leaves, tender stem	Norisocorydine	[65]	39	Bark	Mosin b	[78]
8	Leaves, tender stem, bark	Glaucine	[65,66]	40	Bark	Mosin c	[78]
9	Roots	Liriodenine	[65]	41	Bark	Squamotacin	[78]
10	Leaves, tender stem	Norlaureline	[65]	42	Bark	Molvizarin	[77]
11	Roots	Norushinsunine	[66]	43	Bark	2,4-*trans*-Squamolinone	[79]
12	Roots	Reticuline	[65]	44	Bark	2,4-*cis*-9-Oxoasimicinone	[79]
13	Leaves, tender stem	Roemerine	[67]	45	Bark	Bullacin B	[79]
14	Seeds	Samoquasine A	[68]	46	Seeds	Squamostatin D	[80]
15	Stem	Annosqualine	[68]	47	Seeds	2,4-*cis*-Bullatacinone	[80]
16	Seeds	Cyclosqamosin A	[60,69]	48	Seeds	Squamostatin C	[81]
17	Seeds	Cyclosqamosin B	[60,69]	49	Seeds	Annonin I	[82,83]
18	Seeds	Cyclosqamosin C	[60,69]	50	Seeds	Annonin VI	[82]
19	Seeds	Cyclosqamosin D	[60,69]	51	Seeds	Squamostene-A	[84]
20	Seeds	Cyclosqamosin E	[60,69]	52	Seeds	Reticulacin-1	[20]
21	Seeds	Cyclosqamosin F	[60,69]	53	Seeds	Squamosinin-A	[84]
22	Seeds	Cyclosqamosin G	[70]	54	Seeds	Annotemoyin-1	[20]
23	Seeds	Cyclosqamosin H	[70]	55	Seeds	Notemoyin-2	[20]
24	Seeds	Cyclosqamosin I	[58]	56	Stems	Annomosin A	[20]
25	Seeds	Squamtin A	[71]	57	Stems	Annosquamosins A	[29,46]
26	Seeds	Annosquamosin A		58	Stems	Annosquamosins B	[29,46]
27	Seeds	Annonacin	[72]	59	Stems	Annosquamosin C	[46]
28	Seeds	Annonacin A	[72]	60	Stems	Annosquamosin D	[46]
29	Seeds	Annonastatin	[73]	61	Stems	Annosquamosin E	[46]
30	Seeds	Squamocin	[74]	62	Stems	Annosquamosin F	[46]
31	Seeds	Squamocin-O1	[75]	63	Stems	Annosquamosin G	[46]
32	Seeds	Squamocin-O2	[75]				

TABLE-2
ISOLATED COMPOUNDS WITH THEIR CHEMICAL NAMES OF *Annona squamosa*

S. No.	Chemical structures	Division	Pharmacological activity	Ref.
1	ent-kaur-16-en-19-ol	Diterpenes class		[42]
2	ent-kaur-16-en-19-oic acid	Diterpenes class	Shows toxicity in lung 95-D and ovarian A2780 cancerous cells	[42,43]
3	Ent-kaurane-16β,17,19-triol	Diterpenes class		[42]
4	4α-hydroxy-19-nor-ent-kauran-17-oic-acid	Diterpenes class		[42]
5	16α,17-dihydroxy-ent-kauran-19-oic-acid	Diterpenes class		[42,44]
6	ent-16β,17-dihydroxykauran-19-al	Diterpenes class		[42,44]
7	16β,17-dihydroxy-ent-kauran-19-oic acid	Diterpenes class	Active as anti-inflammatory agent	[42,45]
8	17-hydroxy-16α -ent-kauran-19-oic acid	Diterpenes class		[42,46]
9	17-hydroxy-16β-ent-kauran-19-oic acid	Diterpenes class		[42,46]
10	17-hydroxy-16β-ent-kauran-19-al	Diterpenes class	Inhibits the platelet aggregation	[42,46]
11	17-acetoxy-16β-ent-kauran-19-oic acid	Diterpenes class		[42]
12	19-formyl-ent-kauran-17-oic acid	Diterpenes class		[42]
13	Annosquamosin A	Diterpenes class		[29,42]
14	Annosquamosin B	Diterpenes class	Produces toxicity in lung 95-D and ovarian A2780 cancer cells	[29,42]
15	(4α-)19-nor-ent-kaurane-4,16,17-triol	Diterpenes class		[43]
16	(4α,16α)-17-(acetyloxy)-19-nor-ent-kaurane-4,16-diol	Diterpenes class		[43]
17	17-hydroxy-ent-kaur-15-en-19-al	Diterpenes class	Produces toxicity in lung 95-D and ovarian A2780 cancer cells	[43]
18	ent-15β-hydroxy-kaur-16-en-19-oic acid	Diterpenes class		[29]
19	15,16-epoxy-17-hydroxy-ent-kauran-19-oic acid	Diterpenes class	Shows toxicity in lung 95-D and ovarian A2780 cancer cells	[29]
20	16α, 17-dihydroxy-ent-kauran-19-oic acid methyl ester	Diterpenes class	Toxic in lung 95-D and ovarian A2780 cancerous cells	[29,43]
21	(þ)-anomuricine	Alkaloids class		[47]
22	N-methyl-6,7-dimethoxyisoquinolone	Alkaloids class	Stimulates immune activity	[47,48]
23	N-methylcorydaldine	Alkaloids class		[47]
24	5-((6,7-dimethoxy-2-methyl-1,2,3,4-tetra-hydroisoquinolin-1-yl)methyl)-2-meth-oxybenzene-1,3-diol	Alkaloids class		[49]
25	6,7-dimethoxy-2-methylisoquinol	Alkaloids class		[49]
26	(1R,3S)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline-1,3-diol	Alkaloids class		[49]
27	Anonaine	Alkaloids class		[7]
28	Roemerine	Alkaloids class	Increase the cytotoxic response	[50]
29	Norlaureline	Alkaloids class		[7]
30	Aporphine	Alkaloids class		[7]
31	Norcorydine	Alkaloids class		[7]
32	Corydine	Alkaloids class		[7]
33	Norisocorydine	Alkaloids class		[7]
34	Isocorydine	Alkaloids class		[7]
35	Glaucine	Alkaloids class		[7]
36	(þ)-O-methylarmepavine	Alkaloids class	Stimulates immune activity	[48]
37	Lanuginosine	Alkaloids class	Stimulates immune activity	[7]
38	Dienone	Alkaloids class		[51]
39	-xylopine	Alkaloids class	Inhibits the anococcygeus muscle contraction produced by phenylephrine	[48]
40	Annoglaxin	Acetogenins class		[52]
41	Annoreticuin-9-one	Acetogenins class		[53]
42	Annosquacin A	Acetogenins class		[54,55]
43	Annosquacin B	Acetogenins class	Toxicity in lung A549/Taxol cancer cell bodies	[54]
44	Annosquacin C	Acetogenins class		[54,55]
45	Annosquacin D	Acetogenins class	Toxic in lung A549/Taxol cancer cell lines	[56]
46	Annosquacin-I	Acetogenins class	Produces Toxicity in lung A549, breast MCF-7, liver HepG2 cancer cell lines	[54,55]
47	Annosquamin A	Acetogenins class	Shows toxicity in lung A549/Taxol cancer bodies	[54,55,57]
48	Annosquamin B	Acetogenins class	Produces toxicity in hepatoma H22 and lung A549/Taxol cancer cells	[54]
49	Annosquamin C	Acetogenins class		[54]

50	Annosquatin A	Acetogenins class		[54]
51	Annosquatin B	Acetogenins class	Produces toxicity in hepatoma H22, breast MCF-7, lung A549 cancer cell lines	[55,57]
52	Annosquamosin A	Cyclic peptide class		[58]
53	Cherimolacyclopeptide B	Cyclic peptide class		[59]
54	Cyclosquamosin A	Cyclic peptide class		[60]
55	Cyclosquamosin B	Cyclic peptide class	Possesss vasorelaxant activity	[60]
56	Cyclosquamosin C	Cyclic peptide class		[60,68]
57	Cyclosquamosin D	Cyclic peptide class	Shows anti-inflammatory activity	[59,60]
58	Cyclosquamosin H	Cyclic peptide class		[59]
59	Cyclosquamosin I	Cyclic peptide class		[59]
60	Squamin A	Cyclic peptide class		[59]

list of isolated compounds with their chemical names from *Annona squamosa* exhibiting pharmacological activity are shown in Table-2.

Pharmacological activities

Antioxidant activity: The antioxidant activity of *Annona squamosa* Linn. was proved by investigating the leaf extract for their free radical scavenging potential on different models. The extract was taken with ethanol in1000 µg/mL concentration and tested against various radical cations. Among all these cations it was found that the radical cation 2,2-azinobis- (3-ethylbenzothiazoline-6-sulphonate) undergo maximum scavenging up to 99.07%, nitric oxide radical undergo scavenging up to 73.64% followed by scavenging of 2,2-diphenyl-1-picrylhydrazyl occurred up to (89.77%) at1000 µg/mL concentration. In case of rat-brain homogenate the extract was found to perform only medium scavenging activity on superoxide radical and anti-lipid peroxidation potential. The antioxidant activity of the plant was justified by the study with free radical cations. The aqueous leaf extract of *Annona squamosa* was administered orally to observe the antioxidant effect on serum glucose, blood hemoglobin, glycosylated hemoglobin, insulin, antioxidant enzyme and lipid peroxidation effect on streptozotocin induced diabetic rats particularly in liver and kidney. The serum glucose, lipid peroxidation activity was considerably decreased followed by the enhancement of insulin and antioxidant enzymes in diabetic rats when the aqueous extract was given orally for 30 days. So, finally it was found that insulin and lipid metabolism effect increased by the use of aqueous extract whereas the blood glucose level was gradually decreased. So, the present investigation showed that the aqueous extracts were more desirable free radical scavengers than the non-aqueous extracts and high flavonoid containing leaf extract [66].

Antitumor activity: The antitumor activity of the plant *Annona squamosa* was done by taking the aqueous and organic seed extract and tested on a rat tumor cell AK-5. The apoptosis in cancerous cell was occurred by oxidative stress mechanism due to the division of DNA fragments and staining of annexin-V. The cancerous cell death was occurred prominently followed by the increase in caspase-3 activity due to the effect of organic as well as more polar extract. The significant *in vivo* antitumor activity against AD-5 tumor was confirmed by taking the aqueous extract of plant seeds [2,85]. Due to the *in vitro* and *in vivo* activity of plant seed extract as an antitumor agent for human cells it will hopefully provide a new era for the development of novel antitumor drugs.

Antimalarial activity: The insecticidal as well as larvicidal activity of the plant *Annona squamosa* was proved most commonly against mosquitoes and by taking the ethyl acetate fraction. A comparative study of the ethyl acetate fraction and the parent fraction was done and found that at the same concentration ethyl acetate reduced the activity as compare to the parent one. The present investigation shows the extract comprises of several medium polar compounds those acting synergistically or competitively at the active sites. The larvicidal effect against *Aedes adopictus*, *C. quinqufascinits* and *Annopheles stephensi* were proved in case of plants collected from Brazil. Although from the above study, *Annona squamosa* plant extract emerges as an anti-mosquito agent but a medium activity was found for *Plasmodium falciparum* against a chloroquine sensitive strain and a chloroquine resistant strain [20].

Hepatoprotective activity: The study of aqueous and alcoholic extract of *Annona squamosa* leaves were performed on Wistar strain of rats for the screening of hepatoprotective activity. The experimental animals are devided into treatment group and hepatotoxic group, drugs like isoniazid and rifampicin were used to induce experimental hepatotoxicity and tested against silymarin, the standard or reference drug. After the test it was found the prominent enhancement of total protein whereas gradual decrease in total bilirubin content followed by the decrease in ALP, AST, ALT and δ-GT value in the treatment class in comparison to the hepatotoxic group. The above study revealed that the extract of *Annona squamosa* was not able to treat entirely the isoniazid and rifampicin induced hepatic injury and their reactivity in the liver can be controlled [86].

Antibacterial effect of plant extracts and its usage in wound healing: A number of solvents like alcohol, chloroform and petroleum were chosen and the extraction of *Annona squamosa* leaves was done by using Soxhlet apparatus in order of their sequence of polarity. The cup-plate method was implemented for evaluating the antibacterial activity for all the above extracts. The alcoholic and petroleum ether extracts were choosen for wound healing effect in animals as the zone of inhibition was found to be maximum in these two extracts.Finally, the result revealed that the extracts were the more notable compounds for the wound healing effect after comparing the zone of inhibition result with the control group [87].

Antiarthritic, anti-inflammatory and analgesic activity: The screening was done for testing the anti-inflammatory, antiarthritic and analgesic activities in different experimental animals by taking the combined extract of *Annona squamosa* and *Nigella sativa*. The Complete Freund's Adjuvant (CFA) injection was

administered in metatarsal foot pad of Sprague-Dawley rats to generate arthritis. The paw volume of rats was prominently reduced by the application of the combined extract of plants, decrease in enhanced level of SGOT, SGPT and total protein which is followed by rise in the body mass. The effect of standard drug such as indomethacin and pethidine sulfate were compared with the plant extract to prove their anti-inflammatory and analgesic activity in a particular dose [88].

Antimicrobial activity: Disk diffusion test was being implemented for evaluating the antimicrobial activity of *Annona squamosa* plant extract by taking various solvent for the test. A series of bacteria from both Gram-positive and Gram-negative groups were taken for the examination like *Staphylococcus aureus* and *Bacillus subtilis* and *Escherichia coli*, *Pseudomonas aeruginosa*, respectively. The methanolic extract showed a maximum zone of inhibition for the bacteria *Pseudomonas aeruginosa* with a minimum inhibitory concentration of 130 µg/mL whereas for the extract of petroleum ether the minimum inhibitory concentration was found to be 165 µg/mL for the same bacteria and for methanolic extract the minimum inhibitory concentration was 180 µg/mL in case of Gram-negative bacteria *Escherichia coli* [26].

In another study [89], various solvents like methanol, petroleum ether and aqueous extract were taken to evaluate the antimicrobial activity by agar cup and broth dilution method for different Gram-positive and Gram-negative organism. In this case, a mixed leaf extract of both the plant *A. squamosa* and *A. reticulate* were taken for the test. The above test showed a positive result for methanolic extract with maximum inhibition whereas it is less for other two extracts in each of the plants [89].

Anti-diabetic activity: The *Annona squamosa* leaf extracts were taken with ethanol and evaluated for their hypoglycaemic activity. The extract was administered orally in different proportions to the normal along with the alloxan created diabetic rabbits and streptozotocin created diabetic rats. From the above experiment, it was found that in normal group of animals the fasting blood glucose was declined by 6% whereas the peak blood glucose decreased by 17.17% in case of glucose tolerance test at a proportion of 350 mg/kg body mass. But the result was somehow varied in alloxan created hyper-glycaemic rabbits in the same proportion of ethanolic extract. In this case, fasting blood glucose value was declined to 26.8% whereas peak blood glucose was elevated to 38.5% and 40.6% in case of glucose tolerance test. Lastly, the root extract was taken in aqueous medium and evaluated for the hypoglycemic activity for streptozotocin induced diabetic rats and found reduction in blood glucose from 285.52 to 208.81 mg/dL in a proportion of 250 mg/kg and 500 mg/kg body mass [90,91].

Conclusions

Annona squamosa is a plant available widely in the temperate region which is extensively tested to identify its phytoconstituents and investigated to prove its bioactivity. As the fruit pulp of this plant is edible in nature, it is used as one of the acclaimed materials in food industries. *Annona squamosa* is most widely used in traditional medicine for curing the numerous disease conditions such as diarrhea, inflammation, diabetes, cancer and hyperthyroidism.

It also contains the phytoconstituents like diterpenes, alkaloids, cyclopeptides and annonaceousacetogenins proved by phytochemistry investigations. The plant *Annona squamosa* also shows a number of pharmacological activities like insecticidal, anticancer, hypoglycemic, antioxidant, antimalarial, analgesic and wound healing activity. Among all these alkaloids anonaine induces apoptosis by releasing nitric oxide and reactive oxygen species, energizing caspases and apoptosis-related proteins and destroying the DNA components.

Various plant parts, their extracts and phytoconstituents act by causing the significant tumor cell death with enhances caspase-3 activity. The DNA fragmentation and annexin-V staining may be due to the occurrence of apoptosis in tumor part of the body by oxidative mechanism. The antioxidant activity of plant extract is due to their free radical scavenging potential, while the hepatoprotective action is because of the enhancement of total protein whereas gradual decrease in total bilirubin content followed by the decrease in ALP, AST, ALT and δ-GT value in the treatment class in comparison to the hepatotoxic group. The antiarthritic activity is due to the prominent reduction of paw volume of rats, decrease in enhanced level of SGOT, SGPT and total protein which is followed by rise in the body mass. Mechanism of action of antidiabetic activity includes the decrease in fasting blood glucose and decrease in the peak blood glucose in case of glucose tolerance test.

A comprehensive literature review on the plant *Annona squamosa* has the purpose is to provide encouragement to the research persons to explore and pursue the creative journey for the identification of the phytoconstituents and their broad pharmacological activities and their application in various research field.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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