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Pharmacological Activities of *Annona squamosa*: Updated Review

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Abstract: *Annona squamosa* is a medicinal plant which has been used in alternative medicine from ancient times. Different parts of *Annona squamosa* such as fruits, seeds, leaves and barks have been used to treat many diseases. Some of the active constituents have been identified and investigated for biological actions while the rest are yet to be explored. Current understanding of pharmacological properties of *Annona squamosa* not only supports alternative medicine but also contributes to the development of potential drugs for certain diseases. Therefore, an updated review on pharmacological actions of *Annona squamosa* is in urgent need. The purpose of this review is to provide current understanding of important pharmacological properties of *Annona squamosa*. The information provided in this article could be used to proceed to the designation and development of new pharmacological agents prepared from *Annona squamosa* for commonly encountered diseases.

Keywords: *Annona squamosa*, Pharmacological Activities, Custard Apple, Sugar Apple, Pharmacology

1. Introduction

Annona squamosa is a medium-sized tree which belongs to the family Annonaceae. It grows well in many parts of the world including Asia, Africa, Australia and America. It is well-known with many local names such as sugar apple, custard apple and sweetsop in English, Sirafal in Hindi and Matomoko in Kenya [1].

Recently, much research has been conducted on pharmacological properties of different parts of *Annona squamosa* and has successfully isolated and identified active constituents responsible for therapeutic potential. This has led to the urgent need of an updated review which covers the important pharmacological activities of *Annona squamosa* and the identification of bioactive compounds in a concise and systematic approach.

This review covers the pharmacological properties of different parts of *Annona squamosa* and biologically active constituents responsible for treatment potentials. A considerable attention to the benefits of biologically active chemicals could attribute to the development of potent drugs to certain pathologies.

2. Pharmacological Activities

2.1. Anti-tumor Activity

Cancers are the leading cause of death worldwide. In recent years, researchers have emphasized on the anti-tumor actions of seeds, pericarp and bark of herbs, and active plant chemicals have been identified for their anti-cancer properties [2].

The seed oil exhibits anti-tumor activity in H22 xenograft-bearing mice with a maximal inhibitory rate of 53.54% by oral route. The anti-tumor effect was proved to be downregulation of Interleukin-6/Jak/Stat3 signaling pathway by its main chemical constituents – unsaturated fatty acids [3]. Annonaceous acetogens are recognized anticancer agents from *Annona squamosa* [4]. 12,15-cissquamostatin-A and bullatacin were identified from seed oil and showed significant anti-cancer effects in human cancer cell lines and in H22 cells in mice [5]. Squamoxinone-D was found selectively active against H460 cell line [6].

Squadiolins A and B and squafosacin B are known cytotoxic acetogenins present in *Annona squamosa* seeds.

Squadiolins A and B exhibit significant cytotoxic effect on MDA-MB-231 breast cancer cells. Squafosacin B is also significantly toxic to human Hep G2 and 3B hepatoma and MCF-7 breast cancer cells [7]. Annosquacin A, B and C, annosquatin A and B, and squamostanin A, B and D, squamostolide, bullatacin and uvarigrandin A are other constituents which have antitumor properties [8-11].

The induction of apoptosis is proved to be the underlying mechanism but the seed extract exhibits selectivity for different cancer cells. The extract downregulated Bcl-2 and PS externalization in MCF-7 and K-562 cells while it led to PS externalization in COLO-205 cells [12]. Moreover, free radical generation is thought to be an important mechanism for anti-tumor activity of the seeds. The seed extract not only downregulated Bcl-2 and Bcl(XL) genes but also augmented the production of free radicals in AK-5 histiocytic tumor cells [13].

The pericarp oil of *Annona squamosa* also inhibits tumor growth in SMMS-7721 hepatoma cell line with IC 50 < 55mg/ml. According to GC-MS analysis, the major constituent of the pericarp oil was spathulenol (32.51%). The mechanism of antitumor effect was shown to be pro-apoptosis and cell cycle arrest [14]. Moreover, two entkaurane diterpenoids, ent-kauran-16-en-19-oic acid and ent-kauran-15-en-10-oic acid, of the pericarp oil upregulate Bax and downregulate Bcl-2 and the inhibition is due to the pro-apoptosis and G1 phase arrest [15].16alpha, 17-dihydroxy-ent-kauran-19-oic acid is another cytotoxic chemical present in the pericarp [16].

The bark contains chemical constituents which have cytotoxic properties. Annosquamosin A, B and C, isolated from the bark have been shown to inhibit the growth of 95-D lung cancer cells and A2780 ovarian cancer cells [17]. Treatment with the bark extract also reduced chromosomal aberration and the frequency of micronucleated polychromatic erythrocytes in 7,12 dimethylbenz(a) antracene (DMBA)-induced genotoxicity in hamster models [18]. Moreover, the bark extract reduces lipid peroxidation and potentiates antioxidant activities to inhibit tumor growth [19]. Mosin A, B and C, annoreticuin-9-one, squamotacin, bullacin B, tetrahydrosquamone and bullatacinone have been demonstrated to have cytotoxic activities in different cancer lines [20-23].

The leaf extract of *Annona squamosa* has a potential for treatment of T-cell leukemia/lymphoma. The active constituent known as Lanuginosine exhibited promising cytotoxic effect on HTLV-I infected T-cell lines, MT-1 and MT-2 [24]. O-methylarmepavine and C37 trihydroxy adjacent bistetrahydrofuran acetogenins isolated from the leaves also possess cytotoxic property [25]. In addition, *Annona squamosa* leaf extract has been proved to protect mutations induced by cyclophosphamide [26].

Anticancer effect of *Annona squamosa* demonstrates selectivity for different cancer cells. In the study of Wang and colleagues, crude extract and ethanol acetate extract of *Annona squamosa* had significant anti-tumor actions on human epidermoid carcinoma cell line KB-3-1 and colon cancer cell line HCT-116 but not on hepatocellular carcinoma cell line BEL-7404, lung cancer line H460, prostatic cancer cell line DU145 and breast carcinoma cell line MDA-MB-435 [27]. Both leaf and seed extracts of *Annona squamosa* are active against Jurkat and HL60cell lines [28]. Squamocin P and annosquatin III present in the seeds demonstrate selective inhibitory effect on SMMS 7721/T and MCF-7/ADR cell lines respectively [29].

2.2. Anti-inflammatory Activity

Inflammation is the pathological process that involves cellular components and pro-inflammatory cytokines, and is responsible for the development and progression of several diseases. *Annona squamosa* leaves, pericarp, bark and seeds contain anti-inflammatory chemicals some of which have been identified with possible mechanisms while the rest are still to be investigated.

Annona squamosa leaf aqueous extract counteracted acetic acid-induced colitis in mice by means of oral treatment with 300mg/kg for one month. The extract significantly reduced colonic malondialdehyde (MDA) and significantly increased colonic glutathione (GSH), glutathione peroxidase (GPx) and catalase (CAT) activities [30]. Two new cyclic peptides, fanlizhicyclopeptide A and fanlizhicyclopeptide B isolated from the pericarp of *Annona squamosa* diminish the generation of TNF-α and IL-6 in activated macrophages [31]. In addition, ethanolic extract of *Annona squamosa* decreases CD40 expression and downregulates NF-kB signaling cascade [32].

The 18-acetoxy-ent-kaur-16-ene isolated from *Annona squamosa* bark is responsible for anti-inflammatory and analgesic action at 50 mg/kg dose [33]. Caryophyllene oxide isolated from *Annona squamosa* bark also exerts analgesic and anti-inflammatory at the dose of 12.5-25 mg/kg body weight [34]. 16beta, 17-dihydroxy-ent-kauran-19-oic acid isolated from *Annona squamosa* bark inhibits superoxide production and the release of elastase from activated neutrophils via the inhibition of rapid calcium release from cellular calcium reserve in neutrophils [35].

Regarding anti-inflammatory activity of the seeds, cyclosquamosin D and cherimolacyclopeptide B isolated from *Annona squamosa* seeds inhibit the generation of pro-inflammatory cytokines such as IL-6 and TNF-α in activated macrophages [36, 37].

2.3. Anti-oxidant Activity

Different parts of *Annona squamosa* possess antioxidant properties [38]. Organic and aqueous extracts of *Annona squamosa* leaves showed dose-dependent free radical (1, 1-diphenyl-2-picrylhydrazyl, nitric oxide, and hydrogen peroxide) scavenging activity and reducing power activity [39-43]. The corresponding constituents were suggested to be glycosides, saponins, tannins, flavonoids, and phenols [39].

Oral administration of 5,7,4’ trihydroxy-6,3’ dimethoxy-flavone 5-O-α- I-rhamnopyranoside (THDMF-Rha) isolated from *Annona squamosa* leaves significantly reduced cellular

oxidative stress and raised antioxidant activities in animal models [44]. Another constituent isolated from *Annona squamosa* leaf, quercetin-3-O glycoside, also has antioxidant activity as intake of 15mg/kg/day for 10 days significantly raised the activities of catalase, superoxide dismutase and reduced glutathione [45].

Similarly, methanol and aqueous extracts of the fruit pulp have scavenging actions on DPPH, lipid peroxidation, nitric oxide, superoxides and hydroxyl radicals, ferric-reducing antioxidant power (FRAP) [46, 47]. Furthermore, methanol extract possesses total antioxidant activity (206 µg alpha-tocopherol/g) and reducing power (56µg of ascorbic acid/g) [47]. A newly-discovered water-soluble polysaccharide, ASPW80-1, and its sulfated derivatives, ASPW80-M1, have DPPH and hydroxyl radical scavenging actions and can induce splenocyte proliferation [48].

The seeds also exhibit antioxidant effect. The seeds account for 3201 ascorbic acid equivalent antioxidant capacity g/100 of dry extract [49]. The seed oil contains significant value of total tocopherol [50].

The ethanol extract of the bark is credited with superoxide radical scavenging and DPPH free radical scavenging effects in an experimental study [51].

2.4. Anti-thyroid Activity

5,7,4' trihydroxy-6,3' dimethoxy-flavone 5-O-α- I-rhamnopyranoside (THDMF-Rha) isolated from *Annona squamosa* leaves has been known to be anti-thyroid. The oral intake of the THDHF-Rha at standardized dose for 15 days diminished the I-thyroxine-induced thyrotoxicosis in rats. The effect was comparable to that of propythiouracil [44]. Possible mechanisms are suppression of T4 synthesis and secretion, and inhibition of peripheral deiodenase activity [52].

2.5. Antidiabetic Activity

The extracts of *Annona squamosa* leaves, seeds and roots have antidiabetic and hypoglycemic effect [53-58]. The antidiabetic activity of *Annona squamosa* is contributed by its secretagogue effect, inhibitory effect on alpha-glycosidase and modification of insulin signaling. 100 and 400 mg/kg of the hexane extract increased insulin level and inhibited alpha-glycosidase activity in streptozotocin-induced diabetic mice. The effects were comparable to those of Glimepiride (1mg/kg) and Acarbose (10mg/kg) respectively [59]. Ren and coworkers indicated that acidic heteropolysaccharide known as GASP3-3-I isolated from the fruit pulp is responsible for the inhibition of alpha-glycosidase enzyme [60].

The third mechanism for antidiabetic activity is via the inhibition of protein-tyrosine phosphatase 1B and the enhancement of insulin receptor-beta, IRS-1 phosphorylation and GLUT-4. The net effect is glucose utilization and insulin sensitivity in peripheral tissues [61].

Quercetin-3-O-glucoside isolated from *Annona squamosa* leaf inhibits glucose 6 phosphatase activity in the liver and lowers blood glucose level [45]. *Annona squamosa* leaf extract also decreased blood triacylglycerol and total cholesterol levels in diabetic animals [62]. Combined therapy with *Annona squa*mosa leaf extract and Glipizide was proved to be beneficial in dose reduction of Glipizide up to 50% [63].

2.6. Anti-fungal Activity

Annona squamosa leaves have been stated to possess antifungal properties. Organic and aqueous extracts of *Annona squamosa* processes antifungal activity against important fungal strains – *Alternaria alternate, Candida albicans, Fusarium solani, Microsporum canis and Aspergillus niger* [39]. The active anti-fungal constituents of the leaves are 16-hentriacontanone (palmitone) and 10-hydroxy-16-henriacontanone while squamocin A and G, and squamostatin A are known antifungal chemicals present in the seeds [64].

2.7. Anti-bacterial Activity

Various parts of *Annona squamosa* (leaves, seeds and barks) have been investigated for antibacterial actions against common pathogens commonly encountered in clinical practice. Organisms of food-borne diseases – *Bacillus cereus, Listeria monocytogenes, Staphylococcus aureus and Campylobacter jejuni* are sensitive to leaf extract of *Annona squamosa*. However, the antibacterial effect is heat labile and becomes lost at high temperature [65]. *Neisseria gonorrhoeae* was shown to be susceptible to *Annona squamosa* extract by disc diffusion method and the effect was comparable to those of penicillin and ciprofloxacin [66].

Leaf extract of *Annona squamosa* is also active against *Klebsiella pneumoniae, Streptococcus pneumoniae, Enterococcus faecalis, Staphylococcus epidermidis, Vibrio alginolyticus and Proteus species* [28, 67-68]. All types of leaf extract from *Annona squamosa* exhibit much potent antibacterial actions against Gram-positive bacteria than Gram-negative ones [42]. 16-hentriacontanone (palmitone) which is the major constituent of cuticular wax of *Annona squamosa* leaf is superior in antibacterial action than isomeric hydroxyl ketones [69].

Seed extract of *Annona squamosa* are active against *Pseudomonus aeruginosa* and *Escherichia coli*. Antibacterial constituents present in the seeds of *Annona squamosa* are Annotemoyin-1, Annotemoyin-2, squamocin and cholesteryl glucopyranoside [70]. In addition, flavonoids of *Annona squamosa* was investigated to be antimicrobial in the study of Kotkar and coworkers [71].

The bark of *Annona squamosa* is also active against bacteria. *Bacillus coagulans* and *Escherichia coli* are more sensitive to methanol extract of stem bark than other bacteria [72].

Annona squamosa leaf extract is also a potential leishmanicidal therapy. O-methylarmepavine and C37 trihydroxy adjacent bistetrahydrofuran acetogenins are known chemicals isolated from the leaves, which have IC50 from 23.3 to 37.6 µg/ml against L*eishmania chagasi* [25].

2.8. Anti-viral Activity

16beta-, 17-dihydroxy-ent-kauran-19-oic acid isolated from the fruits of *Annona squamosa* was demonstrated to have antiviral activity against HIV replication in H9 lymphocyte cells with an EC50 value of 0.8 microgram/ml [73]. Meanwhile, further investigations are still needed to understand antiviral property of *Annona squamosa* in some more details.

2.9. Anti-malarial Activity

Leaf ethyl extract of *Annona squamosa* has promising anti-malarial activity against chloroquine-sensitive and chloroquine resistant strains of Plasmodium falciparum [74-76]. N-Nitrosoxylopine, roemerolidine and Duguevalline isolated from *Annona squamosa* leaf extract are known alkaloids responsible for antimalarial properties [77]. Similarly, the bark extract also exhibited IC50 of 30µg/ml against blood stage Plasmodium falciparum [78].

2.10. Immunomodulatory Activity

Resent research has focused on the effects of natural products on immune response of the body. The bark of *Annona squamosa* contains Linuginosine (+)-O-methylarmepavine, Lanuginosine (+)-anomuricinem, Isocorydine and N-methyl-6,7-dimethoxyisoquinolone which can modulate immune response. The mechanism involved are induction of T and B cells to proliferate, stimulation of macrophages, upregulation of CD4+, CD8+ and CD19+ cell population and stimulation of IL-2 and IFN-γ production [79]. Fatty acid ester, (+)-annonlipoxy, also inhibits lipooxygenase activity, thus reducing the quantity of leucotrienes and lipoxins [80].

2.11. Anti-ulcer Activity

Annona squamosa twigs contain active constituents that protect peptic ulcer. (+)-O-methylarmepavine, N-methylcorydaldine and isocorydine have anti-secretory properties. They reduce gastric acidity, pepsin and gastrin level, and inhibit H^+-K^+ ATPase pump. The effect was comparable to that of Omeprazole [81]. This supports the traditional use of the twigs in peptic ulcers. In the same way, *Annona squamosa* leaf extract was shown to be protective against aspirin plus pyloric ligation induced ulcers in mice [82].

2.12. Hepatoprotective Activity

Methanol extract of *Annona squamosa* leaves was found to be hapatoprotective. It ameliorates isoniazid-rifampicin-induced hepatotoxicity in rats with a reflection of restoration in raised liver enzymes ALT, AST, GGT and ALP, serum bilirubin and TBARs level and improvement in total protein and reduced glutathione levels [83, 84]. Similarly, hydroalcoholic seed extract of *Annona squamosa* is demonstrated to be hepatoprotective against CCl-4 induced hepatotoxicity at the doses of 100mg/kg, 200mg/kg and 400mg/kg (extract per body weight) for one week [85].

2.13. Renoprotective Activity

Aqueous extract of *Annona squamosa* leaf has been proved to be renoprotective. Oral intake of 300mg/kg of the extract for one month significantly restored the previously raised urea, creatinine and uric acid levels in streptozotocin-induced diabetic rats. The mechanism is poorly understood but its antioxidant activity may play a role [86]. Another study of Deshmukh and colleagues, consistent findings support renoprotective effect of *Annona squamosa* leaves in renal failure induced by 5/6 nephrectomized animal models. Renal superoxide dismutase activity is increased by the same dose of the extract [87].

2.14. Vasorelaxant Activity

Cyclosquamosin B isolated from *Annona squamosa* seeds possesses vasorelaxant activity. The mechanism is proposed through the inhibition of calcium release from extracellular compartment via voltage-gated calcium channels [88]. However, the therapeutic potential of cyclosquamosin B is currently under investigation.

2.15. Anti-atherogenic Activity

The fresh fruit pulp of *Annona squamosa* has the property to modify plasma lipids, which may be beneficial for cardiovascular risk. Oral administration of 5g/kg body weight reduced total cholesterol by 45-46% in healthy animal models and by 32.4% in alloxan-induced diabetic rabbits [89]. Ent-kaur-16-en-19-oic acid and 16alpha-hydro-19-al-ent-kauran-17-oic acid present in the stem of *Annona squamosa* have antiplatelet property through the inhibition of platelet aggregation [90]. These findings provide the background information on the potential use of *Annona squamosa* for atherosclerosis.

2.16. Antifertility Activity

Ethanol extract of *Annona squamosa* seed powder was reported to have anti-ovulatory activity in rabbits [91]. However, the effect is not promising well enough to be used therapeutically. In animal study of Vohora and colleagues, 200 mg/kg of the seed extract for two days inhibited ovulation in rabbits in 40% [92]. Although some argue that *Annona squamosa* has abortifacient activity, a study in pregnant rats indicated the seed power have no effect on pregnancy [93]. Oral intake of methanol extract of the bark significantly exhibited contraceptive action in male rats but the effect was reversible on discontinuation of the intake of the extract [94].

2.17. Wound Healing Activity

Topical application of ethanolic extract of *Annona squamosa* leaves enhances wound healing by increasing collagen synthesis, glycosaminoglycan synthesis, cellular proliferation at the injured sites [95, 96]. This supports the

ancient topical use of *Annona squamosa* leaves for wounds and ulcers.

3. Conclusion

Different parts of A*nnona squamosa* possess many pharmacological activities – antitumor, anti-inflammatory, antioxidant, anti-thyroid, antidiabetic, antimicrobial, antiulcer, immunomodulatory, hepatoprotective, renoprotective, vasorelaxant, anti-atherogenic, antifertility and wound healing properties. The isolation and identification of the active chemical constituents have put forward the pharmacological and medicinal importance of *Annona squamosa*.

Conflict of Interest

The authors declare that they have no competing interests.

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