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Review Article

Pharmacological Screening of Annona Muricata: A Review

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Abstract

Annona muricata L. (*Annonaceae* family) is a tropical plant and most prominently known for its edible fruit which has more medicinal properties but some effects are toxic. This review most commonly represents the phytochemical contents, pharmacological and biological actions and at some extent toxicological effects which depends on dose, solvent for extraction and part of plant used. More than 200 compounds have been isolated and identify from different parts of this plant. Phenols, alkaloids and acetogenins are the most important and effective compounds. Traditionally, *Annona muricata* is being used to treat diverse ailments such as inflammation, fever, pain, hypertension, diabetes, liver damage, bacterial infection and cancer. Pharmacologically, plant possessed antioxidant, anti-inflammatory, anti-diabetic, anti-hypertensive, anti-nociceptive, anxiolytic, anti-pyretic, wound healing, hepatoprotective, antibacterial, antiviral phyto-chemicals and extracts of this plant have been characterized as hypoglycemic, hepatoprotective, and wound healing activities and cytotoxic, insecticidal, anti-bacterial, anti-viral activities. It could be concluded that the use of *Annona muricata* fruit would be beneficial for having good health.

Keywords: Pharmacological activities, Soursoap, *Annona muricata*

Introduction

Annona muricata L. belongs to *Annonaceae* family and also known as *guanabana, soursoap and graviola* (Moghadamtousi *et al.*, 2015a). *Graviola* fruit is sweet and full of health beneficial components with high moisture content. Flowers are in yellow or greenish-yellow color, solitary and large. Fruit is 18cm long and covered with spine like structure. The pulp is soft white and with agreeable sour flavor (Ross, 2003).

Fourier transform infrared (FTIR) spectrophotometer technique was used for phytochemical analysis and identifies the different structural and functional groups in various extract of *Annona muricata L.* bark. Chemical constituents include phenol, steroids, cardiac glycosides, anthraquinones, phyto sterols, glycosides, tannins, sponins, coumarins, gum in mucilage active constituents and oil steroids (Manigandan *et al.*, 2016).

Medicinally this plant has great importance because of number of pharmacological activities such as anti-mutagenic anti-oxidant, anti-microbial and anti-diabetic (Endrini *et al.*, 2015). The most important pharmacological activity is on sperm toxicity which was evaluate by weight of testes and sperm PH, motility, visibility, epididymal sperm count and epididymis (Ekaluo *et al.*, 2013).

1- **Pharmacological activities:**

1.1 *In-vitro* studies:

Most of *in-vitro* studies correspond to anti-protozoal activity (23%), cytotoxic activity (30%), insecticidal activity (18%) and other remaining 29% activities were confirmed to be anit-microbial, anti-oxidant activity and anti-viral activity (Chaparro *et al.*, 2014).

1.1.1 Mitigating activity:

Sour soap fruit extract (SFE) was evaluated for its mitigating activity against the sperm toxicity induces by overdose of caffeine in albino rats' model. Mitigating activity accessed by weight of testes and visibility, sperm PH, motility, epididymal sperm count sperm head abnormalities and epididymes in mammalian models (Ekaluo *et al.*, 2013).

1.1.2 Anti-viral Effect:

Methanolic extract of *Annona muricata L.* at dose 1mg/kg was evaluated for its anti-viral activity against herpes simplex virus-1 (HSV-1) which is obtain from the keratin lesions of human body. Methanolic extract of *Annona muricata L.* show minimum inhibitory concentration which indicate the anti-HSV-1 activity (Gajalakshmi *et al.*, 2012).

1.1.3 Cytotoxic activity:

Ethanol and water extracts of *Annona muricata L.* leaves and pearl grass was subjected to evaluate the cytotoxic activity against the human breast cancer. Ethanolic extract of *Annona muricata L.* leaves with IC50 values 14.678ug/ml and 88.788ug/ml respectively displayed strongest cytotoxic activity against the Michigan Cancer Foundation-7 (MCF-7) on 24 and 48 hours of experiment as compared to water extract show least cytotoxic activity (Endrini *et al.*, 2015; Najmuddin *et al.*, 2016).

1.1.4 Anti-bacterial activity:

Ethanolic extract of *Annona muricata L.* leaves was screened for its anti-microbial activity against the five different gram +ve and gram –ve bacteria species in agar disc diffusion method. The extract showed highest zone of inhibition against *klebsiella* bacteria 1.6 cm as compared to *proteus* bacteria which show lowest zone of inhibition 0.9cm whereas ethanolic and methanolic extract of *Annona muricata L.* show significant anti-bacterial activity against *staphylococcus aureus* (Chithra *et al.*, 2016).

1.1.5 DNA protective and anti-oxidant activity:

High performance liquid chromatography (HPLC) technique was used to determine the active constituents and total phenolic compounds in methanolic and aqueous extract of *Annona muricata L.* for the DNA protective and free radical scavenging activities against H_2O_2 induce toxicity and by different complementary assay (HRSA, FRAP and DRSA) respectively. Both extract show significant DNA protective activity but the methanolic extract of *Annona muricata L.* revealed the best DNA protective and free radical scavenging activities as compared the aqueous extract (George *et al.*, 2015).

Table 1: *In-vitro* pharmacological activities of *Annona muricata*

Activity	Plant Part	Solvent	Effect	Test Model	Reference
Mitigating activity	Leaves	Methanol	Reduce sperm toxicity	Albino rats	Ekaluo et al., (2013)
Antiviral activity	Stem Leaves Roots	EtOH EtOH	MIC =1mg/ml IC >750 UG/ML IC_{50} =335.85, 248.77, 202.33 ug/ml IC =9 ug/ml	Herpes simplex virus (HSV-1) Spleen cell	(Paarakh *et al.*, 2009) (Gavamukulya *et al.*, 2014) (Pieme *et al.*, 2014)
Cytotoxic activity	Leave Dried fruit Stem seeds	Aqueous, EtOH 40% Aqueous	MIC =2, 7 ug/ml IC > 200ug/ml IC = 4.8ug/ml IC =7.3ug/ml CC50 =24×10-5ug/ml	K562, ECV-304	(Oviedo *et al.*, 2009) (Dai *et al.*, 2011) (Torres *et al.*, 2012) (Betancur-Galvis *et al.*, 1999)
Anti-bacterial activity	Peel Leaves Seeds, stem	Aqueous Aqueous, EtOH Methanolic extract	DIH= 14mm, 50ug/ml DIH =17mm, 50ug/ml MIC >128 ug/ml, MIC > 1024mg/ml, 82% inh 5mg/ml of extract MIC >1024 mg/ml ----------	S.aureus V.cholera S.aureus, E.coli, M. Tuberculosis E.coli, S.aureus	(Viera *et al.*, 2010) (Bussmann *et al.*, 2010) (Radji *et al.*, 2015) (Yasunaka *et al.*, 2005)
DNA protective activity and anti-oxidant activity	Seed juice Leaves Pulp Seed	EtOH MeOH, EtOH EtOH, MeOH EtOH, MeOH	15.75% mort, 6.09 µM of Tr/g IC_{50} = 70ug/ml, 221 ug/ml 280.2 µmol and 160.8 µmol of Tr/100g 306 µmol, 193.4 µmol of Tr/100g	C. gestroiwasmann	(Acda, 2014) (Almeida *et al.*, 2011) (Correa *et al.*, 2012) (Vit *et al.*, 2014)

1.2 *In-vivo* studies:

The most encountered pharmacological in-vivo studies are hypoglycemic activity, gastroprotective activity, anxiolytic and anti-stress activity, anti-hypertensive activity (Bobadilla *et al.*, 2005).

1.2.1 Hypoglycemic activity:

Aqueous and methanolic extract of *Annona muricata L.* leaves at doses 100 mg/kg, orally for 25 day and for two weeks respectively, was evaluated for its anti-

diabetic activity against the streptozotocin induce hyperglycemia in rats. Result showed that both of extract significantly reduce the blood glucose level (4.7 mmol) and (4.22 mmol) by controlling glycemic index (GI) and glycemic load (GL) (Coria-Téllez *et al.*, 2016).

1.2.2 Hepatoprotective and anti-oxidant activity:
Ethanolic extract of *Soursoap* leaves at doses 200-, 400- and 600mg/kg for 8 dayswas assessed for its hepatoprotective and anti-oxidant activity against the 1.6ml carbon tetrachloride 10% intraperitoneally administered to induce liver toxicity which is assigned by elevation of serum glutamate pyruvate transaminase (SGPT) level. Extract significantly reduce the liver toxicity by lowering the SGPT level with an inhibiting value 58.34% in CCL_4induce hepatotoxicity (Tanaya and Dewi, 2015).

1.2.3 Hypolipidemic activity:
Ethanolic and N-hexane extract of *Annona muricata* seeds at doses 10-, 50-, 100-, 1000-, 1500-, 3000- and 5000mg/kg was aimed to assess the acute toxicity in albino rats. Extract within the safe dose ≤5000mg/kg significantly reduce the ($P< 0.05$) LDL, cholesterol, Triglycerol and malondialdehyde level as compared to control group whereas no significant effect assessed in AST, ALT, urea and creatinine level and prove potent agent for the treatment of obesity and chronic heart disease (Nwaneri-Chidozie, 2016).

1.2.4 Gastroprotective activity:
Ethyl acetate extract of *Annona muricata* leaves (EEAM) at doses 200 mg/kg and 400 mg/kg was investigated for its gastroprotective activity against the gastric injury induces by ethanol in rats. Gastroprotective activity assessed by elevate level of agents that attenuate the gastric acidity, such as increase the antioxidant activity and nitric oxide level, including superoxide dismutase, catalase and glutathione (Moghadamtousi *et al.*, 2014).

1.2.5 Anti-inflammatory activity:
Ethanolic extract of *Annona muricata* (AM) leaves was assessed for its acute and chronic anti-inflammatory activity against the xylene induce ear edema and arthritis induce by complete freund's adjuvant (CFA) in mice and rats respectively.Result showed that extract significantly reduceIL-1β and TNF-α leveland also effective for both acute and chronic inflammation (Foong and Hamid, 2012; Moghadamtousi *et al.*, 2015a).

1.2.6 Anti-nociceptive activity:
Ethanolic extract of *Annona muricata* leaves at doses 200mg/kg and 400mg/kg orally was investigated for its anti-nociceptive and anti-inflammatory activity against the intraplantar formalin injection that produces biphasic condition, time licking phase first phase (0-5mins) and second phase (15-30mins) was 86.62±3.18 s and 93.87±2.73 s respectively. After treatment with extract significantly reduce ($P <0.001$) the first phase and second phase at 23.67 and 45.02%, 30.09 and 50.02% respectively (De Sousa *et al.*, 2010).

1.2.7 Wound healing activity:
This study was conducted to evaluate the wound healing activity of ethyl acetate extract of *Annona muricata*at low dose 5%w/w and high dose 10%w/w against wound created on theneck. Extract in ointment form caused significant elevation of antioxidants, decease in malondialdehyde (MDA) level and showed significant wound healing potential (Moghadamtousi *et al.*, 2015b).

1.2.8 Anxiolytic activity:
This study was conducted to evaluate and identify the compounds of *Annona muricata* leaves that prove anxiolytic activity and compare them with pre-existing new anti-anxiety drugs. Aqueous extract of this plant administered to test groups and result showed that active fraction of extract able to prove anxiolytic at low concentration but at high concentration it may prove sedative (Lallier, 2014).

1.2.9 Anti-convulsant activity:
Anti-convulsant activity against the pentylenetetrazol induce attacks of tonic-clonic seizure in different model of mice was evaluated by administration of ethanolic extract of *Annona muricata* leaves at doses 100mgg/kg and 300mg/kg. The result showed extract significantly reduce the mortality rate and incidence of tonic, whereas same doses also lengthen the period of clonic seizure (Moghadamtousi *et al.*, 2015a).

1.2.10 Anti-hypertensive activity:
To investigate the anti-hypertensive activity of *Annona muricata* leaves extract (9.17–48.5 mg/kg) on mean heart rate and arterial pressure on rats. Result showed that extract at dose dependant manner (9.17–48.5 mg/kg) significantly lower the blood pressure

without lowering heart rate. Extract lower blood pressure by affecting the peripheral mechanisms that antagonize the Ca^{+} channel but not mediated through the muscarinic, adrenergic and nitric oxide pathway (Nwokocha *et al.*, 2012).

1.2.11 Anti-parasitic activity:

Anti-parasitic activity of ethyl acetate and methanolic extract of *Annona muricata* was subjected to evaluate against the different pathogenic parasites such as *Leishmania* species and *Trypanosoma cruzi*. Result showed that ethyl acetate extract more effective anti-parasitic as compared to methanol and compare with other extracts and Glucantime® which is used as reference substance (Osorio *et al.*, 2007; Jaramillo *et al.*, 2000).

1.2.12 Anti-plasmodial activity:

Three different extracts (aqueous, ethanol 95% and pentane) of *Annona muricata* leaves powder were prepared by decoction and was subjected to evaluate the anti-plasmodial activity of these extracts against the *P. falciparum*.IC_{50}concentration that inhibits the 50% growth of parasite ranged from 18 µg/ml to 500 µg/ml for aqueous and ethanol 95% extract and for pentane extract ranged from 4.3 µg/ml to 500 µg/ml *(Ménan et al., 2006; Osorio et al., 2007).*

1.2.13 Molluscicidal Activity

Ethanolic extract of *Annona muricata* leaves was evaluated for molluscicidal activity against the egg masses and adult form of *Biomphalaria glabrata.* Extract with dose LD_{90} value of 8.75ppm possess significant toxicity against the adult worms. Extract was manifested to be toxic against the larvae of the brine shrimp *Artemiasalina*and adult forms of the snail *Biomphalaria glabrata* at doses (LC_{50} 0.49 µg mL^{-1}) and (LC_{50} 9.32 µg mL^{-1}) respectively (Dos Santos and Sant'Ana, 2001; Luna *et al.*, 2006).

Table 2: *In-vivo* pharmacological activities of *Annona muricata*

Activity	Plant Part	Solvent	Effect and Dose	Test Model	Reference
Hypoglycemic activity	Leave	Aqueous, MeOH	Reduce blood glucose level (4.7 mmol/l) and (4.22mmol/l) respectively at dose 100mg/kg	Rats	(Adewole and Caxton-Martins, 2006) (Adeyemi *et al.*, 2009)
	Stem	EtOH	Reduce blood glucose (187mg/dl) at dose 100mg/kg	Rats	(Ahalya *et al.*, 2014)
Hepato-protective activity	Leave	Aqueous	97% hepato-protective against CCL4 induce hepatotoxicity at 50mg/kg	Rats	(Arthur *et al.*, 2012)
Hypolipidemic activity	Leave	EtOH and N-hexane	Reduce the ($P < 0.05$) LDL level at safe dose ≤ 5000mg/kg	Albino Rats	(Nwaneri-Chidozie, 2016)
Gastro-protective activity	Leaf	EtOH 80%	Inhibit 92.8% part of gastric lesion at dose 300, 400 mg/kg	Rats	(Hamid *et al.*, 2012)
Anti-inflammatory activity	Laef	Aqueous and EtOH	Plant edema is reduce 71.12% at dose 1.5mg/kg	Mouse model	(Poma *et al.*, 2011)
			Paw edema is by volume (0.47ml) at dose 400 mg/kg	Rats	(De Sousa *et al.*, 2010)

Anti-nociceptive	Leaf	EtOH 80% EtOH	At 10mg/kg prolong reaction time 53.92% At 300mg/kg dose 95.3% inhibit abdominal writhes Acetic acid induce writhing 41.41% reduce at dose 400mg/kg	Mice Mice Mice	Roslida et al. (2012) (De Sousa *et al.*, 2010)
Wound healing	Leave Stem, bark	EtOAc EtOH	77% wound closure in 10% cream Open area of wounds is reduce 88.58% in 4% cream	Rats Rats	(Moghadamtousi *et al.*, 2015b) (Paarakh *et al.*, 2009)
Anxiolytic activity	Leave	EtOH 40%	At 0.5g/kg dose reduce 45% reaction time	Albino mice	(Oviedo *et al.*, 2009)
Anti-convulsant activity	Leave	EtOH	Reduce mortality and tonic-clonic seizure at 100 and 300mg/kg	Mice model	(Moghadamtousi *et al.*, 2015a).
Anti-hypertensive	Leaf	H_2O	57.7mmhg blood pressure is reduce at dose 48.53mg/kg	Rats	(Nwokocha *et al.*, 2012)
Anti-plasmodial activity	Leave	Aqueous, EtOH 95%, Pentane	IC_{50}= inhibit 50% growth of parasite at 500 µg/ml	P-falciparum	(Ménan et al., 2006)
Molluscicidal Activity	Leave	MeOH	LD_{90}=87.5 possess toxicity against adult worm	Adult form of *Biomphalaria glabrata*	(Luna et al., 2006)

2-Toxicology:

Considerable formal and informal information is available in relation of use of *Annona muricata* with an occurrence of an atypical parkinson's disease (Lannuzel *et al.*, 2006). The toxicity reported depends on the plant part used, solvent used for extraction and concentration of extract (Caparros-Lefebvre *et al.*, 2002; Burkill, 1985).

2.1 Acute toxicity:

Ethanolic and methanolic extract of *Annona muricata* leaves, barks and flowers showed acute toxicity LD_{50} >2g/kg and aqueous extract has acute toxicity at dose LD_{50} > 5g/kg these both value considered to be non-toxic under the guideline of OECD (De Sousa *et al.*, 2010). Extract of leaves of this plant at dose 211mg/kg per day can be considered median lethal dose (Arthur *et al.*, 2011). In order to reach lethal dose of S*oursoap* more than 71 cup of tea of this plant must consume during the 24 hours (Arthur *et al.*, 2011). In order to toxicity reported in organ, kidney damage caused by the dose more than 5g/kg of aqueous extract of *Annona muricata* and unlike at dose 1g/kg cause hypoglycemia and Hyperlipidemia (Boyom *et al.*, 2011).

2.2 Neurotoxicology:

On phytochemical study some alkaloids such as Annona cinacetogenins, solamin, Annonacinone and isoannonacinone have shown neurotoxicity of in-vivo and in-vitro study. Annonacin is a phytochemical compound found in *Annona muricata* a potent neurotoxin show 100 times more toxic than 1-methyl-

4-phenylpyridinium (MPP) and 1000 times more potent neuronal cell toxicity (Potts *et al.*, 2012).

Conclusion

Pharmacological investigations of Annona muricata provided scientific based evidence for medicinal properties of this plant. Its consumption as edible fruit is beneficial to keep the person healthy.

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