

A REVIEW ON PHARMACOLOGICAL USES AND MECHANISM OF ACTION OF *AVERRHOA BILIMBI* LINN.

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ABSTRACT

Averrhoa bilimbi, commonly known as bilimbi, is a fruit bearing tree of genus *Averrhoa* and family Oxalidaceae. The fruit, flower and leaves are used in folk medicines for various indications like obesity, hyperlipidemia, diabetes, etc. It's rich various phytoconstituents like saponins, flavonoids, terpenoids etc. It is proved to have various pharmacological actions like antidiabetic, antioxidant, antimicrobial etc. The prime objective of this review is to accumulate and organize articles on *Averrhoa bilimbi* and its proved pharmacological action and its mechanism of action.

Key Words: Bilimbi, *Averrhoa bilimbi*, pharmacological uses, mechanism of action.

INTRODUCTION

Herbal medication had been practiced long before recorded history. Herbal medicines are considered relatively safe with no side effects¹. One such plant with wide range of uses is *Averrhoa bilimbi*. Its leaves and fruits were used traditionally for various indications, in the form of decoction, infusion, fruit juice etc.² *Averrhoa bilimbi* (Bilimbi) is medicinally used as a folk remedy for many symptoms. It is used as antibacterial, antiscorbutic, astringent; post-partum protective medicine. It is also used for the treatment of fever, mumps, pimples, inflammation of the rectum and diabetes, itches, boils, rheumatism, syphilis, bilious colic, whooping cough, hypertension, and stomach ache.

Family: Oxalidaceae

Kingdom: Plantae

PHYTOCONSTITUENTS

Averrhoa bilimbi fruits are rich in flavonoids. Saponins, phenols, coumarins. LC-MS showed the presence of about twenty compounds in the fruits. They are Trans-resveratrol, Umbelliferone, Salicylic acid, Methyl salicylate, Dihydro myrecetin, Eriocitrin, Boswellic acid, Hydroxy aristolochic acid, Cinnamaldehyde, Benzyl cinnamate, Hydroxy-citric acid lactone, Benzyl alcohol, Phenylethyl amine, Leaf Alcohol, Caffeolmalic acid, Citric acid, Tartaric acid, Ascorbic acid, Xylose, Tyrosine⁴.

Averrhoa bilimbi leaves contain aldehyde, sugar and protein and secondary metabolites like cardiac glycoside, flavanoid, alkaloid, phenol, tannin and coumarin while carbohydrate, starch, ketose, fat, amino acid, acid and resins were absent in leaves⁵.

MINERAL CONTENT

Mature fruits of *Averrhoa bilimbi* have potassium and phosphorus in highest quantity and also traces of sodium, magnesium, calcium, zinc, manganese and ferric ions⁶.

VOLATILE COMPONENTS

About Fifty-three volatile components are present in *Averrhoa bilimbi*, among which aliphatic acids are present highest quantity⁷.





PHARMACOLOGICAL USES

ANTIMICROBIAL ACTIVITY

In a study done by Z A Zakaria et al. it was proved that the *Averrhoa bilimbi* has potent antimicrobial activity. Both the leaves as well as the fruits were lethal to wide range of microorganisms. They also compared the antimicrobial activity of aqueous and chloroform extract and aqueous extract was found to be active against Gram positive microorganisms like *S. aureus*, *S. epidermis*, *B. cereus*, *C. diphtheriae*, while the chloroform extract showed potent activity against Gram-positive bacteria like *S. aureus*, *S. epidermis*, *B. cereus*, *K. rhizophila* and *C. diphtheriae*. Both the extracts showed good activity against Gram negative bacteria as well.⁸ In another comparison study done by Md. Abdullah Aziz et.al., water extract of *Averrhoa bilimbi* leaves extract was found to have good antimicrobial property compared to the ethanol and methanol extract of the same⁹. Seri Intan Mokhtar et al studied the antimicrobial property of *Averrhoa bilimbi* at different maturity stages and concluded that the young and mature stages of the fruits has more potent activity against bacteria than the ripe fruits¹⁰.

Mechanism of action

Averrhoa bilimbi is rich in a number of phytochemical constituents. The presence of strong acid such as oxalic acid makes it a potent antimicrobial agent.¹¹ Also the presence of surplus phytochemical is the reason for the antibacterial effects exhibited by the extracts¹².

ANTIOXIDANT ACTIVITY

Antioxidants are the substances which inhibit oxidation. Oxidation is a chemical reaction that can produce free radicals, thereby leading to chain reactions that may damage the cells of organisms. Methanolic extract of *Averrhoa bilimbi* showed a good dose dependent DPHH scavenging activity¹³. The antioxidants property of *Averrhoa bilimbi* is also proved in a in vivo study done in paracetamol intoxicated Wister rats. The antioxidant activity was elucidated by determining the Superoxide dismutase (SOD), Glutathione, Glutathione peroxidase (GPx) levels¹⁴.

Mechanism of action

Averrhoa bilimbi is rich in phenolics compounds such as phenolic acid flavonoids tannins which play a major role in its antioxidant activity¹⁵.

ANTICANCER ACTIVITY

S. Jaghadeesh et al. studied the anti lymphoma activity of *Averrhoa bilimbi* fruit extract on Swiss albino mice. The analysis of haematological parameter and MTT assay proved its anticancer activity. There was a significant reduction in body weight and tumour volume as well as up to 97% inhibition of cell growth in MTT assay¹⁶. The ethanolic leaves extract also have a potent anticancer activity. The anticancer activity of fruit and leaves is proved true for human breast cancer cell lines also. Fruits are more cytotoxic than the leaves¹⁷.

Mechanism of action

Averrhoa bilimbi is rich in phenols, flavonoids, terpenoids, saponins, and steroids. And it is also a good antioxidant agent.¹³ These compounds play a major role in cancer through their effects on signal transduction in cell proliferation and angiogenesis¹⁸.

ANTIDIABETIC ACTIVITY

Averrhoa bilimbi is very effective in normalizing the elevated blood glucose level. The same is proved in streptozocin induced diabetic rats. Administration of *Averrhoa bilimbi* leaf extract reduced the elevated blood glucose level by 50%. Reactive free radicals may be generated as a result of hyperglycaemia induced by the streptozocin, which may lead to peroxidation of lipids. This may ultimately result in increase in the levels of TxA₂ and TxB₂ and thus platelet aggregation. *Averrhoa bilimbi* prevents the platelet aggregation by formation of TBARS (thiobarbituric acid reactive substances (TBARS) Thus it has a hypoglycaemic, hypotriglyceridemic, antiatherogenic, antilipid peroxidation property in streptozocin induced

diabetic rats¹⁹. The *Averrhoa bilimbi* fruits also processes good antidiabetic activity²⁰.

Mechanism of action¹⁹

It is believed to have similar mechanism action as metformin. So it acts by

- Increasing glucose utilization
- Increasing the expression of insulin receptors
- By reducing hepatic gluconeogenesis

HEPATOPROTECTIVE ACTIVITY²¹

Methanolic extract of *Averrhoa bilimbi* also found to have hepatoprotective activity. *Averrhoa bilimbi* showed its hepatoprotective activity by lowering the increased serum marker enzyme and lipid peroxide levels in CCL4 intoxicated rats. It showed a dose dependent action.

Mechanism of action

CCl4 forms free radical which in turn results in membrane damage, increase in serum enzymes such as SGOT SGPT etc. It also results in decrease in antioxidant system such as glutathione (GSH) and hypoalbuminemia as well as hyperbilirubinemia. *Averrhoa bilimbi* has a good antioxidant property. Administration of methanolic extract of *Averrhoa bilimbi* resulted in increase in antioxidant levels such as GSH, which in turn reversed the free radical mediated effects.

CARDIOVASCULAR DISEASES

A study is conducted to study the cardiac contractility and heart rate by Anne Caroline et al. in guinea pigs. And it is found that *Averrhoa bilimbi* reduces the heart rate and atrial contractility²². *Averrhoa bilimbi* also has a good anticoagulant property. It didn't show an immediate action after intake of *Averrhoa bilimbi* as it takes some time to get activated. It is predicted that in future it may be useful in reducing stroke, heart attack, venous thrombosis and other cardiovascular diseases. It can also be used in surgeries to reduce clot formation²³.

Mechanism of action

The exact mechanism by which *Averrhoa bilimbi* reduces clot formation is unknown. But it is assumed that presence of high level of oxalic acid makes it a good anticoagulant agent. Since it is metallic ion chelator it might act by interfering with the action of calcium or sodium mediated thrombin activation. Binding to calcium ions results in prevention of the polymerization of fibrin and inactivation of sodium ions inhibits the subsequent thrombin activation²³.

ANTHELMINTIC PROPERTY

Methanolic extract of *Averrhoa bilimbi* has a very good anthelmintic property. The same is proved in earthworm which has similar physiological and anatomical property as that of intestinal worms. Methanolic extract of *Averrhoa bilimbi* paralysed and then killed the worms in a period less than that of the standard drug that is albendazole. Mechanism by which it acts as anthelmintic agent is unknown²⁴.

ANTIMALARIAL ACTIVITY

Methanolic extract of *Averrhoa bilimbi* leaves has been proved for its antimalarial action. It showed a dose dependent inhibition of parasite *plasmodium faciparum* invitro. For this cultured *plasmodium faciparum* were used which were incubated with human serum for blood smear preparation. It is considered to have a good antimalarial activity since the IC50 value was less than 10µg/ml. It showed a good activity at a concentration as low as 2.805µg/ml with action increasing with concentration.

Mechanism of action

The antimalarial property of *Averrhoa bilimbi* is due to the presence of a flavonoids- Luteolin which is soluble in methanol. It acts on the Fab 1 enzyme and inhibits it, resulting in the inhibition of fatty acid chain extension cycle. This results in the inhibition of growth of *P. falciparum*²⁵.

DENTAL BLEACHING AGENT

Bleaching refers to restoration of a natural tooth shade. They are used in case of teeth discoloration hydrogen peroxide and carbamide peroxide are bleaching agents most often used. The bleaching property of *Averrhoa bilimbi* is proved invitro by *Cut Fauziah et al.* Both qualitative and quantitative data suggested that the *Averrhoa bilimbi* has potential to change the colour of enamel, but the result obtained was less than standard chemical bleaching agent carbamide peroxide²⁶.

Further studies are conducted by I M Msandi et al. to test enamel colour change effect of extract of *Averrhoa bilimbi* fruit in the form of gel. The study was done in bovine incisive teeth. It proved that application *Averrhoa bilimbi* extract gel which was prepared using carboxymethyl cellulose at different concentration resulted in discoloration of teeth to brownish yellow colour²⁷.

Mechanism of action

The presence of peroxide and oxalate acid is believed to be the reason for tooth whitening property of *Averrhoa bilimbi*.

ULCERATIVE COLITIS²⁸

Ulcerative colitis is an inflammatory bowel disease that causes long lasting inflammation and ulcers. Ulcerative colitis affects the innermost lining of the colon and rectum. The effect of *Averrhoa bilimbi* fruit extract on ulcerative colitis was studied using Wistar albino rats. There was a decrease in mucosal ulcers and inflammatory mediators level in *Averrhoa bilimbi* treated rats compared to control.

Mechanism of action

Averrhoa bilimbi is a very good antioxidant agent which is believed to be the reason behind the protective effect against ulcerative colitis. NO level decreased while SOD and GSH level was found to be increased in colon region.

GINGIVAL WOUND HEALING PROPERTY²⁹

Gingival wound healing is an important process as it prevents the further microbial infection. Increase in fibroblast level is considered as an index of wound healing. It showed a dose dependent action with highest activity at a concentration from 10 to 20%, while the action decreased at higher concentration.

Mechanism of action

Immediately after tissue injury various pathways get activated and synchronized to prevent infection. The cells involved in wound healing include immune system cell such monocytes, lymphocytes, endothelial cells, keratinocytes and fibroblasts. These cells undergo massive fluctuations in gene expression, resulting in important changes in cell proliferation, differentiation and migration. After *Averrhoa bilimbi* administration there was more increase in fibroblast level compared to control indicating the wound healing property of *Averrhoa bilimbi*.

HYPOLIPIDEMIC ACTIVITY^{30, 31, 32}

Flower, fruit as well as fruit extract of *Averrhoa bilimbi* has hypolipidemic activity. 400mg/kg of leaves extract of *Averrhoa bilimbi* showed a response similar to, and in some parameter better response than standard drug in streptozocin induced diabetic rats. The hypolipidemic activity of *Averrhoa bilimbi* flowers has also proved in-vitro. In case of fruits only the fruit and water extract of fruit showed to have activity, while alcohol and hexane extract did not show any hypolipidemic activity. The action showed by fruit is independent of dose at 125mg/kg and 250mg/kg while water extract showed an increase in activity from 25 to 50mg/kg but further increase in dose resulted in decline in

the activity. Further the active constituents were isolated using various solvents from the soluble portion of alcohol precipitate of the water fruit extract. In that, ethyl acetate fraction gave a good result at a lower concentration compared to butanol and aqueous fraction. All of these parts showed a decrease in cholesterol levels like LDL, TG and total cholesterol and increase in good cholesterol HDL.

Mechanism of action

Averrhoa bilimbi has flavonoids, tannins, terpenoids and phenols. The synergistic action of these constituent might be the reason for antihyperlipidemia.

OXIDATIVE STRESS³³

Ethyl acetate extract of *Averrhoa bilimbi* is effective in reducing oxidative stress due to diabetes. The same is proved by estimation of serum glucose, glycated haemoglobin, plasma insulin, hydroperoxides. Even the histopathology of liver also showed protective effect against oxidative damage.

Mechanism of action

Presence of Quercetin might be the reason behind its protective effect against oxidative stress.

OTHER USES**RIPENING OF FRUITS³⁴**

Masilungan, G.D et al. proved the ripening effect of *Averrhoa bilimbi* in Saba banana. Presence of bilimbi fruit hastened the ripening of the banana compared to control. While injured bilimbi fruit further hastened the ripening. *Averrhoa bilimbi* produces Ethylene which accounts for its ripening activity.

TOXICITY³⁵

Intake of highly concentrated *Averrhoa bilimbi* fruit juice results in renal injury. This is due to the high oxalate content of the fruits.

CONCLUSION

The presence of various constituents like saponins, terpenoids, flavonoids, quercetin etc contribute to the various pharmacological action of *Averrhoa bilimbi*. Studies have been done on fruits, leaves as well as flowers of bilimbi. It is a very good anti diabetic, Antihyperlipidemic, antimicrobial, hepatoprotective, anthelmintic, antioxidant, agent. Further it is found to be useful in malaria, gingival wound healing etc. Further detailed studies are required to elucidate its beneficiary effect on various diseases. But administration of higher concentration of *Averrhoa bilimbi* fruit for a prolonged period of time is injurious to kidney.

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