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Antifungal Activity of Organometallic Complexes of Cholic Acid

Tripathi Kishu

Smt Vidyawati College of Pharmacy, Jhansi, India.

ABSTRACT

Cholic acid & metal ions both have antifungal activity , therefore, their organometallic complexes were prepared to have synergistic effect. Cholic acid is one of the lead molecule for preparing organometallic complexes & their complexes were found to have more active antifungal activity than the cholic acid.

Key words: Cholic acid, Organometallic complexes

INTRODUCTION

Cholic acid, a main bile acid, is a biosurfactant involved in the digestion of dietary lipids .It is commercially available at low cost. Furthermore , it has an unusual molecular structure with some special characteristics, such as the facial amphiphilicity . The carboxylic acid & three hydroxylic groups can act as synthesis handles. For these reasons cholic acid is a suitable building block for new functional molecules.

Cholic acid, a natural biodetergent has been reported to exhibited antibacterial [11-14], antiviral[5], antifungal [4], antimalarial [10] , antitubercular[10], anticancer[9], spermicidal[2, 3] , antiallergic [6,7,8] etc. Since cholic acid is a suitable building block for new molecules or in other words, it is a lead compound for the development of various compounds, therefore, it is thought worthwhile to select it for the above research work.

The antimicrobial activity of metal chelates was found to be in the order[1]:

$Cd^{II} > Ni^{II} > Mn^{II} > Cu^{II} > Zn^{II} > Co^{II} > Fe^{II}$

Cholic acid is one of the lead molecule for preparing organometallic complexes & their complexes were found to have more active antifungal activity because of synergistic effect of cholic acid as well as metal ions.

The present work divulge that formation of cholic acid metal complexes results in synergistic effect i.e., antimicrobial activity of metal complexes of cholic acid have higher activities than the cholic acid. Thus, it leads to possibility of novel class of metal based fungicidal agents.

MATERIALS AND METHODS

The antifungal activity of organometallic compounds of cholic acid was based on Poisoned Food Technique [15, 16, 17] and done against *Aspergillus flavus* and *Aspergillus niger* collected from NBRI, Lucknow. The antifungal activity of

these compounds was tested by agar plate diffusion method using Ketoconazole as standard and 10, 20 , 50 , 100µg/ml of compounds.

Procedure:
The compounds were prepared and tested against *Aspergillus flavus* and *Aspergillus niger*. The one ml of each compound of particular concentration was poured into a Petridishes having about 20-25 ml of molten potato dextrose agar medium. As the medium gets solidify, Petri dishes were inoculated at the centre of plate separately with the fungal isolates and kept at 37°C for 96 hours in BOD incubator. All the values (zone of inhibition, % inhibition) was recorded by known mathematical calculation.

Detection:
Antifungal activity of organometallic compounds of cholic acid was measured from zone of inhibition, % inhibition. (Table 1)

Table 1: Antifungal Activity of Organometallic Compounds of Cholic Acid

Compound Code	Concentration (µg/ml)	Aspergillus flavus (dia.mm)	% Inhibition	Aspergillus niger (dia.mm)	% Inhibition
CCL-VII	10	1.4	53.3	1.5	25.0
	20	1.2	60.0	1.2	40.0
	50	1.0	66.6	0.8	60.0
	100	0.8	73.3	0.5	75.0
AN-VIII	10	1.2	60.0	1.4	30.0
	20	1.0	66.6	1.0	50.0
	50	0.8	73.3	0.8	60.0
	100	0.5	83.3	0.4	80.0
LA-IX	10	1.4	50.3	1.4	30.0
	20	1.2	60.0	1.2	40.0
	50	1.0	66.6	0.5	75.0
	100	0.8	73.3	0.2	90.0
CON-X	10	1.2	60.0	1.0	50.0
	20	1.0	66.6	1.0	50.0
	50	0.6	80.0	0.5	75.0
	100	0.4	86.7	0.2	90.0
BN-XI	10	1.4	60.0	1.0	50.0
	20	1.2	66.6	1.0	50.0
	50	1.0	80.0	0.5	75.0
	100	0.8	86.7	0.2	90.0
CDN-XII	10	0.8	73.3	1.4	30.0
	20	0.6	80.0	1.2	40.0
	50	0.4	86.7	0.5	75.0
	100	0.2	93.3	0.2	90.0
CUA-XIII	10	1.4	53.3	1.5	25.0
	20	1.0	66.6	1.0	50.0
	50	0.7	76.6	0.6	70.0
	100	0.4	86.7	0.1	95.0
CUS-XIV	10	1.4	53.3	1.0	50.0
	20	1.0	66.6	0.8	60.0
	50	0.7	76.6	0.5	75.0
	100	0.4	86.7	0.2	90.0
CA	10	1.2	60.0	1.0	50.0
	20	1.0	66.6	0.8	60.0
	50	0.8	73.3	0.5	75.0
	100	0.5	83.3	0.2	95.0
Control	100	3.0	-	2.0	-

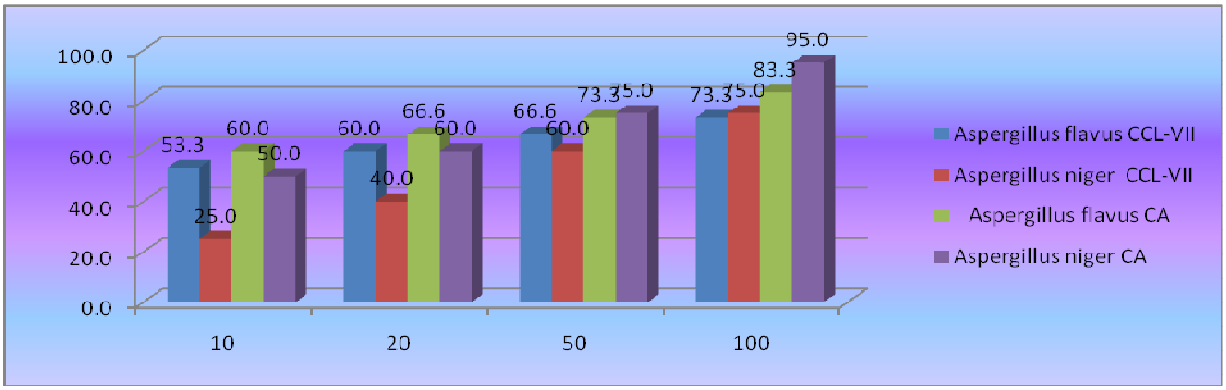

Figure:1 Antifungal Activity of CCL-VII

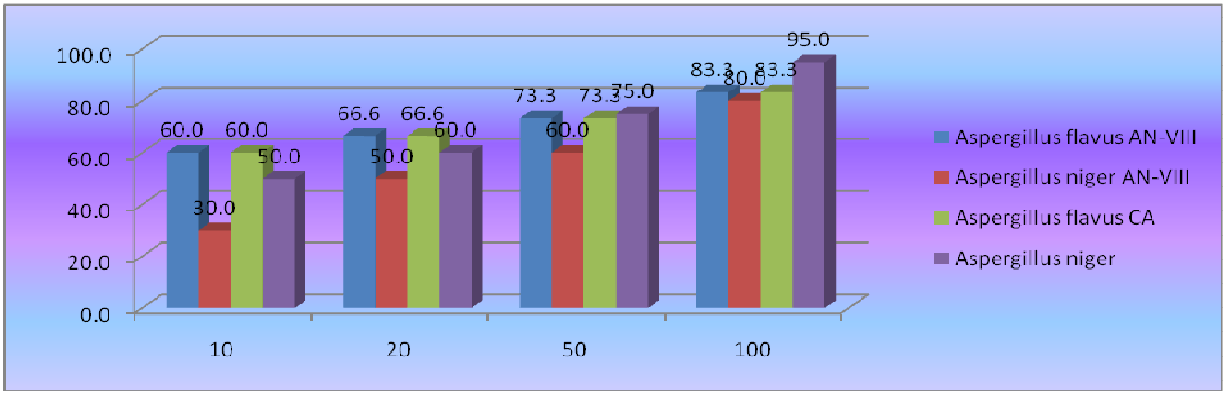

Figure:2 Antifungal Activity of AN-VIII

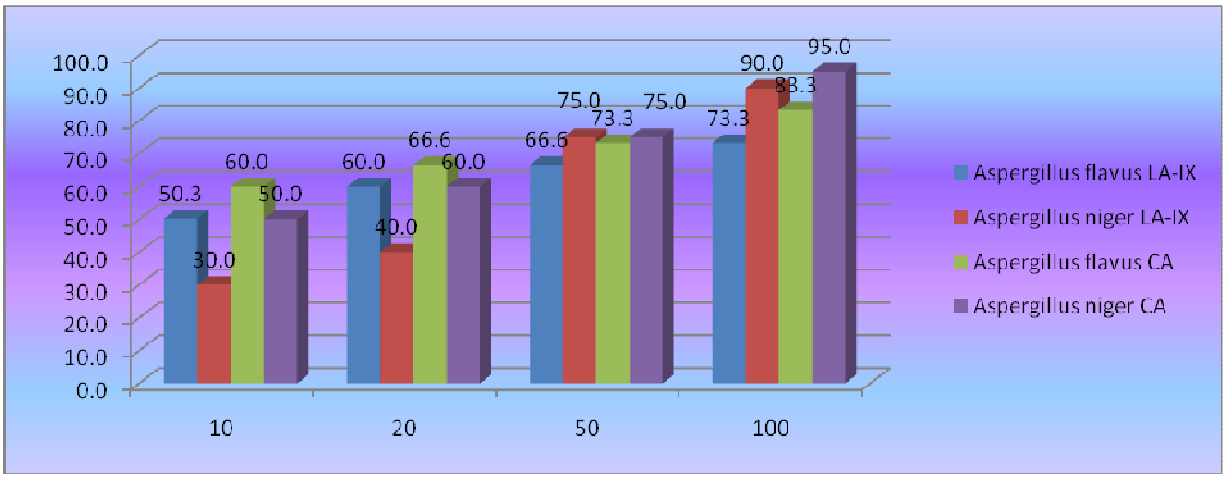

Figure:3 Antifungal Activity of LA-IX

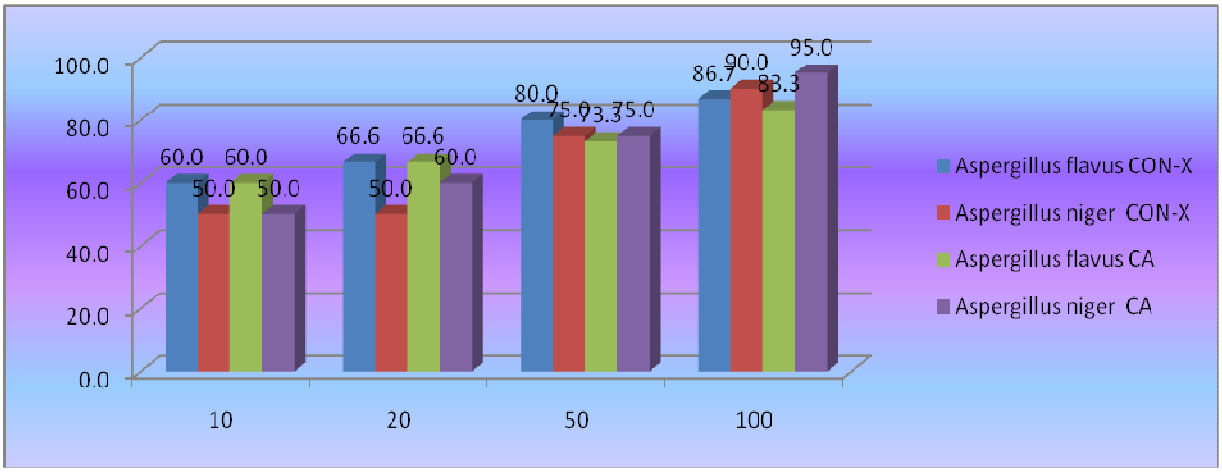

Figure:4 Antifungal Activity of CON-X

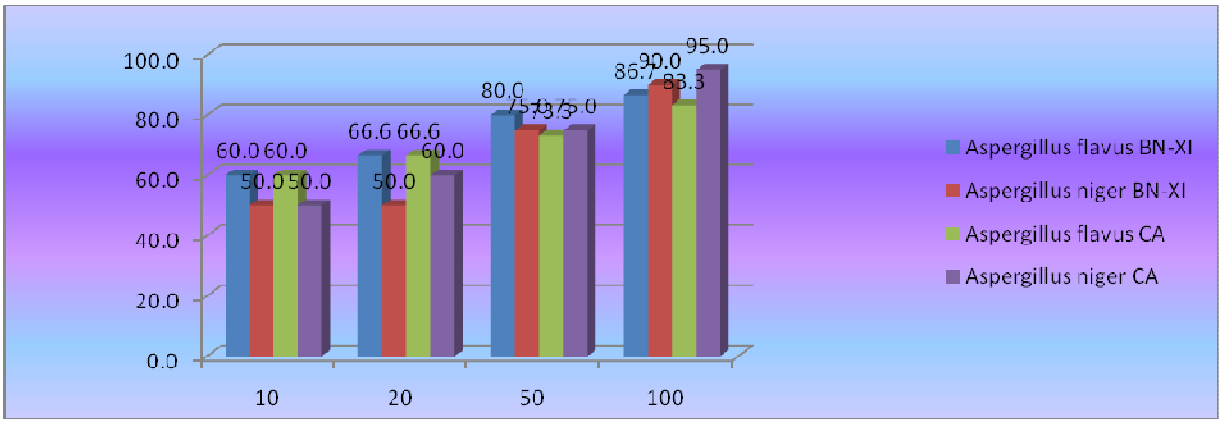

Figure:5 Antifungal Activity of BN-XI

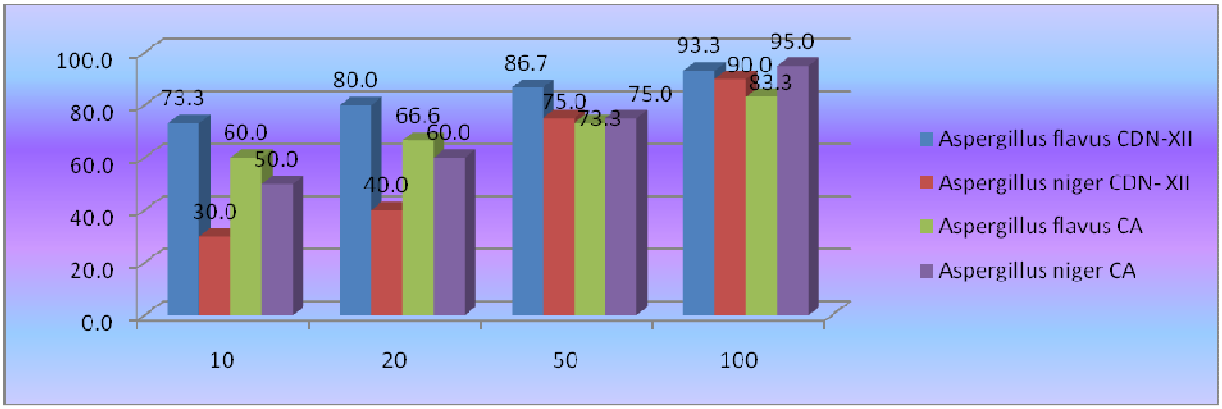

Figure:6 Antifungal Activity of CDN-XII

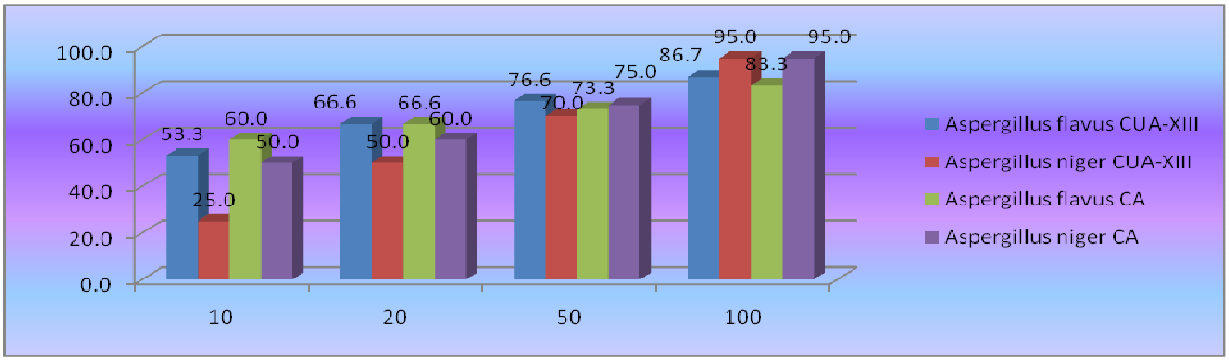

Figure:7 Antifungal Activity of CUA-XIII

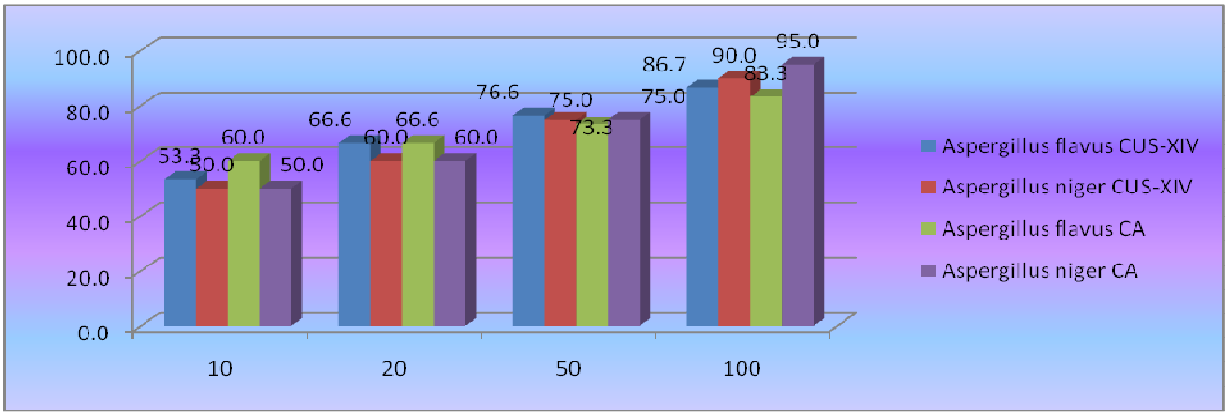

Figure:8 Antifungal Activity of CUS-XIV

RESULTS

% inhibition of CCL-VII (Cobalt Chloride) against Aspergillus flavus is more than CA i.e cholic acid & is more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of AN-VIII (Silver Nitrate) against Aspergillus flavus is equal or slightly more than CA i.e cholic acid & is more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of LA-IX (Lead Acetate) against Aspergillus flavus is slightly more than CA i.e cholic acid & is more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of CON-X (Cobalt Nitrate) against Aspergillus flavus is equal or slightly less than CA i.e cholic acid & is equal or slightly more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of BN-XI (Bismuth Nitrate) against Aspergillus flavus is equal or slightly less than CA i.e cholic acid & isequal or more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of CDN-XII (Cadmium Nitrate) against Aspergillus flavus is less than CA i.e cholic acid & is equal or more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of CUA-XIII (Copper Acetate) against Aspergillus flavus is more at 10 µg/ml & equal or slightly less at 20 µg/ml,50 µg/ml & 100 µg/ml than CA i.e cholic acid & is more against Aspergillus niger than CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & 100 µg/ml.

% inhibition of CUS-XIV (Copper Sulphate) against Aspergillus flavus is more at 10 µg/ml & equal or slightly less at 20 µg/ml,50 µg/ml & 100 µg/ml than CA i.e cholic acid & is equal against Aspergillus niger to CA i.e cholic acid at 10 µg/ml,20 µg/ml,50 µg/ml & is more against Aspergillus niger than CA i.e cholic acid at 100 µg/ml.

DISCUSSION

Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues. Changing hydrophilicity and lipophilicity probably leads to bring down the solubility and permeability barriers of cell, which in turn enhances the bioavailability of chemotherapeutics on one hand and potentiality at another.

Cholic acid & its metal complexes are one of the novel group among the metallic complexes having following characteristics:

1)Good antibacterial as well as antifungal activity.
2)Metal chelates have a higher activity than the free ligand.

Aforesaid increased activity of the metal chelates can be explained on the basis of Overtone's concept and Tweedy's chelation theory. According to Overtone's concept of cell permeability the lipid membrane that surrounds the cell favours the passage of only lipid soluble materials due to which liposolubility is an important factor that controls antimicrobial activity. On chelation, the polarity of the metal ion is reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups & increases the delocalisation of π-electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of metal binding sites on the enzymes of the microorganism. Metal complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organisms.

The inhibition of microbial growth by cholic acid & its complexes with divalent metallic salts was found to be in the following order:

$Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} < Zn^{2+} < Cd^{2+}$

The result showed that the activity enhanced from Mn^{2+} to Cd^{2+} as charge density increases due to electrons draining from metal to ligand by back donation facilitating the intramolecular hydrogen bonding between coordinated ligands and slowly approaching the chelating character, which subsequently favor lipophilic nature of central metal ion in permeation through the lipid layer of membrane.

$Cd^{2+,}$ Zn^{2+}, Cu^{2+} and Ag^{1+} complexes possess high degree of inhibition which may be attributed to the greater number of d-electrons, which increases the electrostatic field around metal ion.

CONCLUSION

Organometallic complexes of Cholic acid exhibits more antifungal activity than Cholic acid alone i.e they exhibit synergistic antifungal activity. Thus, it leads to possibility of novel class of metal based fungicidal agents.

Future prospects of the above research work is that it is hoped that the chemistry of the synthesized complexes of cholic acid would contribute to the better understanding of them as antifungal agents and possibility of pharmacological studies in view of new findings in the present work. However, the further studies needed for the molecular level and toxicity.

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