

Multifunctional activities of several polyoxometalate compounds prescription on RNA virus replication and bacillus multiplication

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Abstract

Polyoxometalates (PM) are discrete oligometric anions of early-transition metal oxides such as tungsten (W), molybdenum (Mo), vanadium (V), antimony (Sb) oxides. Various biological effects of PM have been studied on antitumor, antiviral, and antibacterial activities. For discovery with multifunctional drug in infectious disease, we selected as anti-MRSA, anti-VRSA, and anti-RNA virus what has an effect from these activity compounds, and did mixed prescription. The mixed prescription of PM compounds (MPM) are shown below: (1) V1: $VOSO_4$. (2) V2: $K_{11}H(W)_3(SbW_9O_{33})_2$. (3) W1: $Na_9[SbW_9O_{33}]$. (4) O1: oxacillin. (5) P1(Irgasan): 5-Chloro-2-(2,4-dichlorophenoxy) phenol. The each PM were synthesized according to literatures and did not chemical reaction their self. The MPM were examined about anti-Influenza virus and anti-constant bacillus activities. The MPM inhibited Influenza virus replication and constant bacillus multiplication. Further more, the MPM inhibited multiplication of Escherichia coli and fungus also. PM compounds are act as a direct inhibitor and enhancer of oxacillin or Irgasan. The MPM are useful as a sterilization antiseptic. Now, the goods which sprayed this MPM on the steamed towel or the paper towel are developed.

Introduction

Polyoxometalates (PMs) have been investigated in the course of study of their medical applications. Polyoxometalates (PM) are discrete oligometric anions of early-transition metal oxides such as tungsten (W), molybdenum (Mo), vanadium (V), antimony (Sb) oxides. Various biological effects of PM have been studied on antitumor, antiviral, and antibacterial activities. For discovery with multifunctional drug in infectious disease, we selected as anti-MRSA, anti-VRSA, and anti-RNA virus what has an effect from these activity compounds, and did mixed prescription.

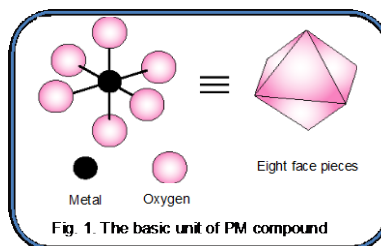


Fig. 1. The basic unit of PM compound

Results

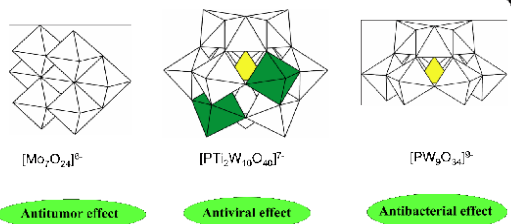


Fig. 2. Biologically-active polyoxometalates

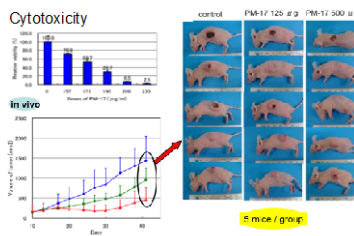


Fig. 3. The effect on the pancreatic cancer of PM compound (Reference data)

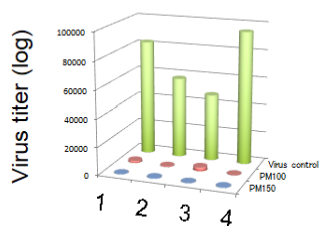


Fig. 4. Prevention of Influenza virus on MPM

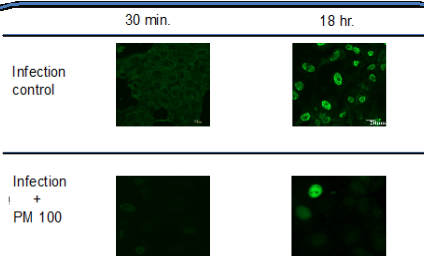


Fig. 5. Detection of virus nucleic protein in infected cells using microscopic imaging. The state of virus penetration in infected cells was observed with a confocal laser scanning microscope using FITC-labeled Abs of nucleocapsid protein of influenza virus.

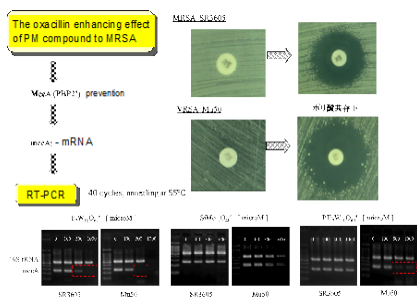
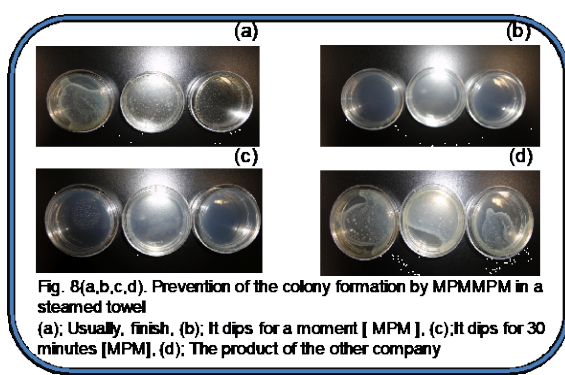
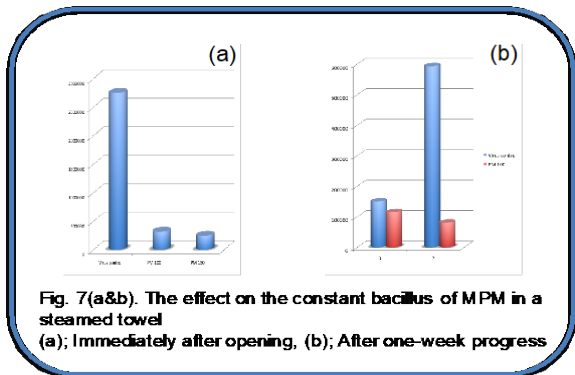


Fig. 6. The oxacillin enhancing effect of PM compound to MRSA

Table 1. Anti-bacillus effects of MPM

Classification	The kind of bacillus	MIC (ppm)
Gram positive bacteria	Staphylococcus aureus	0.1
	Streptococcus faecalis	10
	Bacillus subtilis	1
Gram negative bacteria	Escherichia coli	3
	Proteus Vulgaris	1
	Salmonella typhi	1
	Shigella dysenteriae	3
	Salmonella choleraesuis	1
Fungus	Trichophyton floccosum	10
	Epidermophyton floccosum	10
Mold	Peonicillium citrinum	10
	Candida albicans	10

MIC: Minimum inhibitory concentration



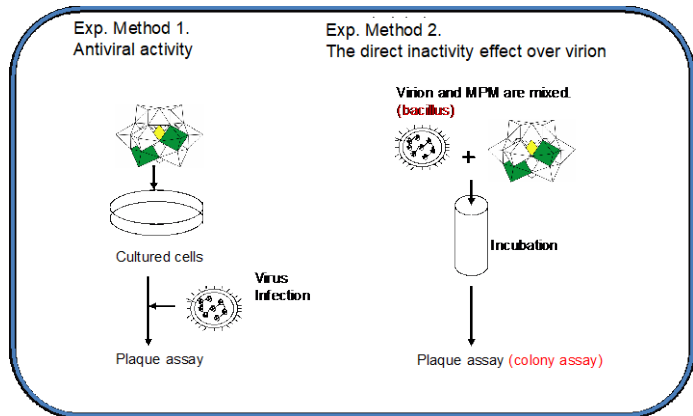
- 1) PM compound made 8 face piece structures the basic unit (Fig.1.), various space structure was made, and it became clear that biological activity differs, respectively (Fig. 2.).
- 2) In PM compound, what shows an effect to a pancreatic cancer is clear (Fig.3.).
- 3) MPM can reduce multiplication of an influenza virus to about 1% or less (Fig.4.). It was proved also from virus nucleic protein hardly being detected in a cell, either (Fig. 5.).
- 4) MPM enhances the antibacterial activity of an antibiotic (Oxacillin) further (Fig. 6.).
- 5) Irgasan blended with MPM has an antibacterial effect which attains to a variety in a very small quantity extremely (Table 1.).
- 6) Also when MPM was added to a steamed towel, these antibacterial properties and an antiviral effect were held. Furthermore, the effect was maintained for a long period of time (Fig. 7&8).

Discussion

- * The MPM is a mixture of the five kind of compounds which had biological activity in each. Mutually [MPM], prevention was not carried out but the synergistic effect was accepted rather.
- * The MPM inhibited Influenza virus replication and constant bacillus multiplication.
- * Further more, the MPM inhibited multiplication of Escherichia coli and fungus also.
- * PM compounds are act as a direct inhibitor and enhancer of oxacillin or Irgasan.

Materials & Methods

The mixed prescription of PM compounds (MPM) are shown below:
 (1) V1: VOSO4. (2) V2: K11H(W)3(SbW9O33)2. (3) W1: Na9[SbW9O33]. (4) O1: oxacillin. (5) P1(Irgasan): 5-Chloro-2-(2,4-dichlorophenoxy)phenol.
 The each PM were synthesized according to literatures and did not chemical reaction their self. The MPM were examined about anti-Influenza virus and anti-constant bacillus activities.



Conclusions

The mixed prescription of PM compounds (MPM) possessed multifunctional activities on RNA virus replication and bacillus multiplication. Each structure material of MPM has activity respectively, and does not inhibit mutual activity. A synergistic effect, not to mention it, is shown. By adding MPM to a steamed towel or a paper towel, it can become antibacterial properties with high safety, and antiviral products.

要約 (和訳)

RNAウイルス複製および細菌増殖に対する数種ポリオキソメタレート配合物の多機能活性

ポリオキソメタレート(PM)はタングステン(W)、モリブデン(Mo)、バナジウム(V)、アンチモン(Sb)酸化物などの初期遷移金属酸化物のオリゴメトリックアニオンである。PMの抗腫瘍、抗ウイルス、抗菌に対する種々な生物活性が研究されてきた。感染症における多機能性薬剤による発見のために、これらの活性化合物から効果のある抗MRSA、抗VRSA、抗RNAウイルス剤を選択し、混合処方を行った。PM化合物(MPM)の混合処方を以下に示す:

(1) V1: VOSO₄。

(2) V2: K₁₁H(W)₃(SbW₉O₃₃)₂。

(3) W1: Na₉[SbW₉O₃₃]

(4) O1: オキサシリン (抗生物質)

(5) P1(イルガサン): 5-クロロ-2-(2,4-ジクロロフェノキシ)フェノール (抗菌剤)

各PMは文献に従って合成され、それらの自己化学反応はおこさなかった。

MPMは抗インフルエンザウイルスおよび抗一般生菌活性について検討した。

MPMはインフルエンザウイルスの複製と恒常的な桿菌増殖を阻害した。

さらに、MPMは*Escherichia coli*および真菌の増殖も阻害した。

PM化合物はオキサシリンまたはイルガサンの直接的阻害剤およびエンハンサーとして作用する。

MPMは抗菌剤として有用である。

現在、このMPMを蒸しタオルまたはペーパータオルに噴霧した製品が開発されている。

* 現在は(4)(5)を排除し、新たな配合(1)(2)(3) & PHMBによる特許化合物に改良されている。

解説

* MPMの基本構造をなすPM化合物は遷移金属元素の周りに酸素が6個または8個配位した基本骨格となる (Fig.1)。またこれらの酸素どうしが共有結合することにより多彩な立体構造をとり、さらに大きなクラスター構造を構成する。

* これら化合物の生物活性における長年の研究から、立体構造と生物活性の間に構造活性相関があることが突き止められた (Fig.2)。すなわちどのような立体構造をとるかによって、がんにも効果を発揮するもの、ウイルス、菌にも効果があるものが想定できる状態になった。

* 抗腫瘍活性化合物では、すい臓がんにも効果を発揮する化合物も発見され、その効果がマウス腫瘍モデルにおいて実証されている (Fig.3)。

* 抗ウイルス活性化合物 (今回のMPM; 100μg/ml以上) ではインフルエンザウイルスに対して99.99%の抑制効果が認められた (Fig.4)。(試験管レベルで感染価、10万のウイルスをほぼ完全に抑制した。)

* その作用部位を検討したところ、ウイルスが細胞に吸着侵入する感染初期の過程で効果を発揮することも突き止められた (Fig.5)。

* MPMはそれぞれに役割を持った配合物で、MRSA(メチシリン耐性黄色ブドウ球菌)に対する効果が実証された (Fig.6)。また幅広い範囲の抗菌効果も有する (Table.1)。

* おしぼりの最終液にMPMを配合した場合、開封直後のみならず、1週間経過しても抗菌効果が持続していたことが示されている (Fig.7)。

* おしぼりの洗浄時間として、瞬間的に与えた場合も、30分間浸した状態でも同様に抗菌活性が示され、他社の通常洗浄ではえられない効果であった (Fig.8)。