Original Article

Novel regimens of phytopolyphenols with cisplatin or memantine and ZnSO₄ for synergistic inhibition of growth and gingipains of the cultured *Porphyromonas gingivalis*

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**Abstract**  **Background/purpose:** *Porphyromonas gingivalis* (P.g.) played a keystone pathogen not only in initiation and progression of periodontitis but also as a risk factor involved in systemic diseases (Alzheimer’s disease, cancers, diabetes, osteoporosis etc.). Developments of effective and safe drugs to inhibit P.g. growth are urgent. In this study, we aimed at approaching novel regimens so called (PTM) by combination of repurposing drugs including phytopolyphenols (P) (curcumin, tea polyphenols), targeting drugs (T) such as cisplatin or memantine and metal ions(M) (ZnSO₄).

**Materials and methods:** The synergistic (combination Index (CI) < 1) antiproliferation and anti-protease efficacies (IC₅₀) of novel regimens on cultured P.g. were evaluated by OD600 and colorimetric method respectively.

**Results:** The results obtained revealed that these novel regimens (PTM) synergistically (combination index, CI < 1) exerted not only antiproliferative but also anti-gingipain protease effects of P.g. The concentrations for 50% inhibition (IC₅₀) of novel regimens on P.g. growth and gingipains were greatly decreased as compared with those of cisplatin or memantine alone.

**Conclusion:** Since these novel regimens exerted potent anti-bacterial effects on both planktonic and biofilm P.g., it is encouraged for further preclinical and clinical trials.

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Introduction

Porphyromonas gingivalis (P.g.) is known not only as a keystone pathogen of periodontal diseases\(^1\)\(^-\)\(^2\) but also involved in the etiology of systemic diseases\(^3\)\(^-\)\(^5\) such as cancers, atherosclerosis, osteoporosis etc., especially Alzheimer’s disease (AD).\(^6\)\(^-\)\(^8\) Thus, investigation of effective and safe novel regimens against P.g. growth especially against P.g. biofilm is urgent. In our previous experiments, tea polyphenols were found to synergistically enhance the inhibitory effect of memantine against neuroexcitotoxicity.\(^8\)\(^-\)\(^10\) Furthermore, both tea polyphenols and curcumin possessed antibacterial effects. Thus, in this study, we attempted to explore the novel regimens not only against P.g. growth but also anti-protease activities of P.g. The strategy to design compositions of novel regimens was to combine phytopolyphenols (P) and targeting drugs (T), either cisplatin\(^11\)\(^-\)\(^13\) (cis, the commonly used anticancer drug) or memantine\(^14\)\(^-\)\(^16\) (mem, for therapy of moderate AD) and metal ions (M) such as ZnSO\(_4\)\(^17\)\(^-\)\(^19\) (antibacterial and immune-modulating agent), so called PTM regimens. We investigated these PTM regimens on the growth and gingipain protease inhibition of planktonic and biofilm P.g. The results obtained indicated the synergistic effects of these novel regimens against P.g. growth and protease activities. These novel regimens appeared to be promising and encouraging for further preclinical and clinical investigations.

Materials and methods

Drugs studied

Curcumin (C) was purchased from Merck Co. (Darmstadt, Germany). Green tea polyphenols purified from Camellia sinensis containing 98% polyphenols (75% catechins HPLC and 50% EGCG HPLC) similar to polyphenol E\(^20\) was purchased from Hunan Huacheng Biotech, Inc., China. Cisplatin and memantine were from Sigma Chemical Company (St. Louis, Missouri, USA).

Culture of Porphyromonas gingivalis

The anaerobic pathogen, Porphyromonas gingivalis, (P.g.), ATCC 33277 was cultured in LB (Luria–Bertani) broth supplemented with hemin (5 \(\mu\)g/ml) and menadione (1 \(\mu\)g/ml) at 37 ± 0.5°C in the anaerobic chamber containing 10% H\(_2\), 5% CO\(_2\) and 85% N\(_2\), Forma Scientific Inc., Marietta, OH, USA.\(^21\)

Anti-microbial effects of drugs on the proliferation of Porphyromonas gingivalis (P.g.)

The proliferation rate of the cultured P.g. was measured by Elisa reader (BioTek’s Epoch™ Micro-Volume Spectrophotometer System) at optical density 600 nm (OD600).\(^21\) After 16 h culture, the OD600 value of cultured P.g. was adjusted to about 0.1. The effects of the drugs on P.g. proliferation was evaluated by the changes of OD600 after addition of various concentrations of drugs (10 \(\mu\)l/well) to 90 \(\mu\)l/well of the cultured bacteria diluted with cultured broth by fold at OD600 about 0.06 in 96 well microplate. The drug effects were evaluated after 24 h incubation with the bacteria by changes of OD600 and then calculated as percentage of the control treated with vehicle saline. The experiments were carried out in triplicate. The antibacterial potency of the drugs was quantitatively by the concentration inhibition curves and calculated the concentration of each drug for 50% inhibition (IC50).\(^21\)

The synergistic antimicrobial effect of various drug combinations as compared with that of drug alone were assessed by combination index (CI).\(^22\)

\[
CI = \frac{(IC_{50})_1\text{ in combination}}{(IC_{50})_1\text{ alone}} + \frac{(IC_{50})_2\text{ in combination}}{(IC_{50})_2\text{ alone}} + \frac{(IC_{50})_3\text{ in combination}}{(IC_{50})_3\text{ alone}}
\]

CI < 1, synergism; CI = 1, addation; CI > 1, antagonism

Potency ratio(fold) = \(\left(\frac{(IC_{50})_1\text{ alone}}{(IC_{50})_1\text{ in combination}} + \frac{(IC_{50})_2\text{ alone}}{(IC_{50})_2\text{ in combination}} + \frac{(IC_{50})_3\text{ alone}}{(IC_{50})_3\text{ in combination}}\right) \times \frac{1}{3}\)

| Drugs | IC50 (\(\mu\)g/ml\(\mu\)g/ml\(\mu\)M) | CI | Potency |
|-------|---------------------------------|----|---------|
| C     | 113.1 ± 8.6                     |    | 3.3     |
| GC    | 87.3 ± 9.1·87.3 ± 9.1           | 1.0| 5.7     |
| Cis   | 10.6 ± 1.0                      | 0.8| 12.1    |
| Mem   | 146.6 ± 8.5                     | 0.8| 12.2    |
| Zn    | 443.3 ± 16.7                    | 0.7| 12.1    |
| CCis  | 65 ± 2.82.2 ± 0.1               | 0.8| 2.3     |
| GCcis | 57.4 ± 2.457.4 ± 2.41.8 ± 0.1   | 0.8| 2.3     |
| CMem  | 59.2 ± 1.459.2 ± 1.4            | 0.9| 2.9     |
| GCMem | 50 ± 2.350 ± 2.350 ± 2.3        | 0.9| 2.3     |
| CisZn | >550                            | >0.6| <5.5    |
| MemZn | 128.8 ± 10.6·43.1 ± 3.6         | 1.0| 5.7     |
| CZn   | 104 ± 10.2·34.6 ± 3.4           | 1.0| 6.9     |
| GCZn  | 67.5 ± 4.0·67.5 ± 4.0·20.6 ± 1  | 0.8| 11.4    |
| CCisZn| 49.5 ± 2.3·14.4 ± 0.215.2 ± 1  | 0.6| 12.9    |
| GCCisZn| 48 ± 1.8·48 ± 1.8·16 ± 0.2    | 0.7| 12.1    |
| CMemZn| 49.5 ± 2.1·49.5 ± 2.1          | 0.8| 11.4    |
| MemZn | 15.4 ± 0.7                      | 0.8| 12.2    |
| GCMemZn| 42.8 ± 2.3·42.8 ± 2.3           | 0.8| 12.2    |

C, curcumin; GC, green tea polyphenols plus curcumin; Cis, cisplatin; Mem, memantine; Zn, ZnSO4.

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1. Alzheimer’s disease
2. Cancer
3. Atherosclerosis
4. Osteoporosis
5. Polyphenol E
6. Phytopolyphenols
7. Memantine
8. Cisplatin
9. ZnSO4
10. Porphyromonas gingivalis
11. LB broth
12. OD600
13. IC50
14. Combination index
15. Potency ratio
16. Mosquitoes
17. Cisplatin
18. Memantine
19. ZnSO4
Effects of drugs on biofilm formation of Porphyromonas gingivalis (P.g.)

The cultured P.g. was incubated with various concentrations of drugs anaerobically at 37 ± 0.5 °C for 48 h. The effects of drugs on biofilm formation were evaluated by changes of OD600 values. Concentrations of drugs for 50% inhibition (IC50) and their synergistic effects were assessed as described previously.

Table 2  Antibiofilm formation (IC50) of novel regimens of cisplatin and memantine on the cultured Porphyromonas gingivalis (P.g.).

| Drugs          | IC50  (µg/ml:µg/ml:M) | CI | Potency |
|----------------|-----------------------|----|---------|
| C              | 122.9 ± 7.9           |    |         |
| GC             | 92.7 ± 7.0-92.7 ± 7.0  |    |         |
| Cis            | 44.9 ± 3.4            |    |         |
| Mem            | 175.5 ± 11.2          |    |         |
| Zn             | 438.2 ± 15.6          |    |         |
| CCis           | 77 ± 3.7-2.6 ± 0.2    | 0.7 | 9.6     |
| GCCis          | 90.4 ± 8.9-90.4 ± 8.9 | 1.0 | 8.4     |
| CMem           | 78.2 ± 1.9-78.2 ± 1.9  | 1.1 | 1.9     |
| GCMem          | 62.8 ± 3.1-62.8 ± 3.1 | 1.0 | 2.1     |
| CisZn          | >5-50                 | >0.2| >8.9    |
| MemZn          | 243.7 ± 47.9-81.9 ± 16 | 1.6 | 3.0     |
| CZn            | 111.5 ± 5.3-37.2 ± 1.8 | 1.0 | 6.4     |
| GCZn           | 85.7 ± 7.2-85.7 ± 7.2 | 1.0 | 8.9     |
| CisZn          | 104.9 ± 1.2-3.2 ± 0.1 | 1.0 | 9.7     |
| MemZn          | 243.7 ± 47.9-81.9 ± 16 | 1.6 | 3.0     |
| CisZn          | 94.4 ± 3.4-94.4 ± 3.4 | 1.2 | 9.7     |
| MemZn          | 59.6 ± 4.9-59.6 ± 4.9 | 0.9 | 9.5     |
| CisZn          | 76.7 ± 5.7-67.6 ± 5.7 | 1.2 | 7.9     |
| MemZn          | 67.6 ± 5.7-72.4 ± 1.8 |     |         |

C, curcumin; GC, green tea polyphenols plus curcumin; Cis, cisplatin; Mem, memantine; Zn, ZnSO4.

Effects of drugs on arg-gingipain protease activities of Porphyromonas gingivalis (P.g.)

After drug treatments for 48 h on P.g. biofilm formation, the protease activities of P.g. biofilm was assayed by the hydrolysis of the protease substrate, 0.5 mM N-α-benzoyl-arg-p-nitroanilide at 37 °C for 30 min. The protease activities were evaluated by measurement of colored product at OD405 as described.

Statistics

Results for each experiment were represented as mean ± SEM. One way ANOVA followed by a post-hoc t test was used to evaluate differences between the groups. The level of significance was defined as P < 0.05.

Results

Tables 1 and 2 described the potencies (IC50) of drugs either alone or in combinations on the inhibitions of the proliferations of planktonic or biofilm formation of cultured Porphyromonas gingivalis (P.g.) respectively. Curcumin(C), tea polyphenols plus curcumin (GC), cisplatin (Cis), memantine (Mem) and zinc (ZnSO4) all inhibited P.g. proliferation in both planktonic and biofilm nearly equally except that Cis was less potent about 4 times on biofilm formation as compared to that on planktonic P.g. (Tables 1 and 2). The important findings were that the combination of phytopolyphenols (C or GC) with either Cis or Mem exhibited synergistic antiproliferative effects (CI < 1) on both planktonic and biofilm P.g. respectively. Furthermore, two of those novel regimens plus ZnSO4 (C-Cis-Zn and GC-Cis-Zn) enhanced synergistically (CI < 1) much better antiproliferative potencies to about twelve and nine times on planktonic and biofilm P.g. respectively (Tables 1 and 2). On the other hand, ratios of IC50 values of Cis used alone over those in the novel regimens were mostly within four and fourteen times on planktonic and biofilm P.g. respectively (Fig. 1A), suggesting that the antiproliferative potencies of Cis were greatly increased and thus the...
concentrations of Cis could be greatly decreased which would certainly increase the safety and decreased the side effects of Cis.

Similarly, the novel regimens of Mem, also synergistically (CI < 1) or additionally (CI = 1) enhanced the anti-proliferative effects on planktonic and biofilm P.g., respectively (Tables 1 and 2). The ratio of IC50 of Mem used alone over those in novel regimens were within 2–3 times on planktonic and biofilm P.g., respectively (Fig. 1B).

Table 3 indicated IC50 of all drugs either alone or novel regimens in anti-protease effects on biofilm P.g. Most of the novel regimens also exhibited synergistic anti-protease effects (CI < 1). The ratios of IC50 of Cis (Fig. 2A) and Mem (Fig. 2B) used alone over those in novel regimens mostly were greater than 200 times and 4 times respectively, with the exception of Cis-Zn and Mem-Zn.

**Table 3** Anti-protease effects (IC50) of novel regimens of cisplatin and memantine on the cultured *Porphyromonas gingivalis* (P.g.) biofilm.

| Drugs   | IC50 (μg/mL μg/mL μM) | CI   | Potency |
|---------|-----------------------|------|---------|
| C       | 245 ± 19.1            |      |         |
| GC      | 63.5 ± 0.5–63.5 ± 0.5  |      |         |
| Cis     | 418.0                 |      |         |
| Mem     | 340.7 ± 4.6           |      |         |
| Zn      | 437.6 ± 2.0           |      |         |
| CCis    | 66.72.2               | 0.3  | 96.8    |
| GCCis   | 48.9 ± 0.1–48.9 ± 0.1–11.6 ± 0.0 | 0.8  | 131.3   |
| CMem    | 71.9 ± 6.3–71.9 ± 6.3  | 0.5  | 4.1     |
| GCMMem  | 37.5 ± 1.3–73.5 ± 1.7  | 0.7  | 5.4     |
| CisZn   | >550                  | >0.1 | <46.2   |
| MemZn   | >150–50               | >0.6 | <5.5    |
| CZn     | 81.4 ± 3.6–27.1 ± 1.2  | 0.4  | 9.6     |
| GCZn    | 60.2–60.2 ± 19.9      | 1.0  | 11.5    |
| CCisZn  | 66.6 ± 5.2 ± 2.1 ± 11.7 ± 1.7 | 0.3  | 75.9    |
| GCCisZn | 52.9 ± 6.9 ± 1.3 ± 17.6 | 0.9  | 86.1    |
| CMMemZn | 79.6 ± 1.8–79.6 ± 1.8  | 0.6  | 8.0     |
| GCMMemZn| 53.3 ± 5.5–53.3 ± 5.5  | 1.0  | 10.7    |
| C, curcumin; GC, green tea polyphenols plus curcumin; Cis, cisplatin; Mem, memantine; Zn, ZnSO4. |

**Discussion**

In this study, we have successfully composited the novel regimens containing phytopolyphenols (curcumin, C; tea polyphenols, G) and cisplatin (C-Cis, GC-Ccis) or memantine (C-Mem, GC-Mem) or in additional with ZnSO4 (C-Cis (Mem) Zn; GC-Cis (Mem) Zn) for antibacterial agents. These regimens exhibited potent inhibitions on the growth of the keykeystone pathogen *Porphyromonas gingivalis* (P.g.), which could orchestrate the host-commensal microbiota homeostasis into dysbiosis, leading to the initiation and progression of the chronic inflammatory periodontal diseases.1,2

Thus, the effective and safe drugs to combat P.g. growth are urgently needed. Fortunately, the novel regimens studied in this paper showed promising not only synergistic antibacterial effects but also anti-gingipain protease activities of P.g. Considering these repurposing drugs being effective and safe, it is encouraged to explore the possibility of these novel regimens for clinical managements of periodontitis, cancer and Alzheimer’s diseases.

In our laboratory, we have studied the biological effects of phytopolyphenols (curcumin, tea polyphenols etc.) for more than 30 years.26–29 Both curcumin and tea polyphenols possessed antioxidant, anti-inflammatory, anti-carcinogenicity, immune-modulatory, antibacterial and neuroprotective effects. Moreover, both curcumin30–33 and tea polyphenols34,35 were shown to be the promising antibacterial agents for the therapy of periodontitis. Thus, these natural products combined with Cis or Mem especially further combined with ZnSO4 (an antibacterial and immunomodulatory agent) against P.g. growth were proofed to be promising novel regimens.

Most importantly, these phytopolyphenols inhibited gingipain protease activities of P.g., especially they synergistically inhibited these enzyme activities in the novel regimens. Since gingipains were important virulence factors of P.g. to subvert the host immune complement responses and for...
inducing inflammatory and proteolytic hydrolysis of connective tissues to provide nutritional supplements to themselves as well as to the opportunistic pathogens in the polymicrobial synergy dysbiosis.36,37 These findings further confirmed their potentiality of novel regimens to clinical applications.

In conclusion, developments of antibacterial agents on P.g. are urgent for therapeutic managements of periodontitis and many systemic diseases (cancer, Alzheimer’s disease etc.). The novel regimens studied in this paper apparently revealed the advantages as P.g. antagonists including: (1) All drugs are repurposing both effective and safe. (2) The synergistic effects of the drugs in the novel regimens in both antibacterial and anti-protease activities. (3) Multiple targeting regimens and pleiotropic pharmacological effects may combat the problem of occurring drug resistance. These preliminary results merits for further preclinical and clinical investigations.

Declaration of competing interest
The authors have no conflicts of interest relevant to this article.

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