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Compressed Mints and Chewing Gum Containing Magnolia Bark Extract Are Effective against Bacteria Responsible for Oral Malodor

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Flavors and natural botanic extracts are often used in chewing gum and compressed mints for breath freshening and relief of oral malodor. The oral malodor is a result of bacterial putrification of proteinaceous materials from food or saliva. In this study, magnolia bark extract (MBE) and its two main components, magnolol and honokiol, were evaluated by the minimum inhibition concentration (MIC) test. The inhibitory effect of MBE mint was further evaluated by a kill-time assay study. In addition, an *in vivo* study was performed on nine healthy volunteers postlunch. Saliva samples were taken before and after subjects consumed mints and gum, with and without MBE. Listerine mouthwash was included as a positive control. The testing results indicated that MBE and its two main constituents demonstrated a strong germ-kill effect against bacteria responsible for halitosis and also *Streptococcus mutans*, bacteria involved in dental caries formation. The MIC of magnolol, honokiol, and MBE on *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *S. mutans* ranged from 8 to 31 μg/mL. Kill-time assay results indicated that mints containing 0.2% MBE reduced more than 99.9% of three oral bacteria within 5 min of treatment. The *in vivo* study demonstrated that MBE containing mints reduced total salivary bacteria by 61.6% at 30 min and 33.8% at 60 min postconsumption. In comparison, the flavorless mint reduced total salivary bacteria by 3.6% at 30 min and increased total bacteria by 47.9% at 60 min. The MBE containing chewing gum reduced total salivary bacteria by 43.0% at 40 min, while placebo gum reduced total salivary bacteria by 18.0%. In conclusion, MBE demonstrated a significant antibacterial activity against organisms responsible for oral malodor and can be incorporated in compressed mints and chewing gum for improved breath-freshening benefits.

KEYWORDS: Magnolia bark extract; oral malodor; compressed mint; chewing gum; *Porphyromonas gingivalis*; *Fusobacterium nucleatum*; *Streptococcus mutans*

INTRODUCTION

Oral malodor, also referred to as bad breath or halitosis, is a major social and psychological problem that affects the majority of the general population (*1*). Volatile sulfur compounds (VSCs), such as hydrogen sulfide, methyl mercaptan, and dimethyl sulfide, are the principal materials that impart oral malodor. The malodorous volatile sulfur compounds are generated through the metabolic activities of oral microorganisms on substrates available in the oral cavity. Gram-negative bacteria, predominantly at the dorsum of the tongue, are considered to be the most important group of microorganisms in the production of oral malodor (*2*–*6*).

Chewing gum and compressed mints are often used by consumers for breath freshening to relieve oral malodor. Technologies for the treatment of oral malodor include using flavors to mask bad breath, zinc and copper salts to chelate volatile sulfides, and antimicrobial compounds to reduce the levels of halitosis bacteria.

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In the past few years, many antimicrobial agents have been developed for the inhibition of halitosis bacteria and, thus, for the treatment of oral malodor (*7*–*10*). Antibacterial compounds, such as chlorhexidine, cetylpyridinium chloride, triclosan, and chlorine dioxide, have been tested either alone or in different combinations. However, most agents have been known to induce side effects. For example, chlorhexidine stains the teeth. Triclosan was found to react with free chlorine in drinking water to form toxic substances in a recent study (*11*).

Magnolia bark extract (MBE) is a traditional Chinese medicine isolated from the stem bark of *Magnolia officinalis*. It is traditionally extracted by steam and hot water decoction or by organic solvent extraction. Recently, it was extracted by carbon dioxide supercritical fluid extraction. The CO_2-extracted MBE consists of primary magnolol and honokiol and a slight amount of essential oils. MBE is used in traditional Chinese medicines for the treatment of fever, headache, pain relief, and stress reduction (*12*). MBE was recently shown to have antimicrobial activity against *Helicobacter pylori*, which plays a critical role in the pathogenesis of gastritis and peptic ulcers

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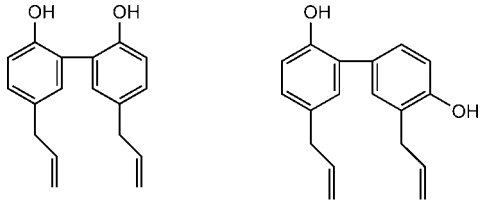

Magnolol Honokiol

Figure 1. Chemical structures of magnolol and honokiol isolated from *M. officinalis*.

(*13*). It was shown to inhibit *Propionibacterium acne* that causes skin inflammation (*14*). MBE was also shown to inhibit the growth of *Porphyromonas gingivalis* (*15*). Unlike synthetic antimicrobial compounds, recent toxicology studies showed that MBE has very low toxicity and fewer side effects (*14, 16, 17*).

The objective for this study was to determine (1) the antimicrobial activity of MBE on oral bacteria responsible for oral malodor and (2) whether gum and mints can deliver MBE and provide antimicrobial activity *in vivo*.

MATERIALS AND METHODS

Chemicals. Magnolol (5,5′-di-2-propenyl-(1,1′biphenyl)-2,2′-diol) and honokiol (3′,5-di-2-propenyl-(1,1′-biphenyl)-2,4′diol) were purchased from Waco Chemicals (Japan). MBE was received from Masson Pharma (China) without further purification. The MBE contains 94% magnolol and 1.5% honokiol. **Figure 1** shows the chemical structures of magnolol and honokiol. A total of 20% of chlorhexidine gluconate solution was obtained from Spectrum Chemical (Gardena, CA) and diluted in sterile water to serve as a positive control for the *in vitro* antimicrobial tests. Other chemicals were received from Aldrich Chemicals (Milwaukee, WI). Bacterial strains were obtained from the American Type Culture Collection (ATCC, Rockville, MD). All media were obtained from Defco.

The sugarless gum and compressed mints used in this study were prepared in the Wrigley laboratory. For compressed mints, the Eclipse and Extra Peppermint mints with 0.2% MBE and without MBE were prepared. The piece weight was 0.7 and 1.1 g for Eclipse mint and Extra mint, respectively. For chewing gum, the MBE level was 0.067% MBE and was formulated either in the center or coating layer. The piece weight of gum was 1.5 g.

High-Performance Liquid Chromatography (HPLC) Analysis of MBE. The composition of MBE was analyzed by HPLC following the method reported in the literature (*18*). An Agilent, model 1100, equipped with a variable ultraviolet (UV) detector was used. The wavelength of the UV detector was set at 209 nm. A Waters Nova Pack C-18 column was employed. The column temperature was set at 35 °C with a flow rate of mobile phase at 1.0 mL/min (CH_3CN/H_2O, 50:50 volume ratio).

For analysis of the release of MBE from gum, 3 g of gum containing MBE was chewed by each of the six subjects separately for 0, 6, 12, and 20 min, respectively. The gum bolus from each subject/time was expectorated. The bolus was dissolved in chloroform and analyzed for MBE by HPLC. The percentage of MBE retained in gum was calculated using an external standard method and a calibration curve.

***In Vitro* Antibacterial Assay.** The *in vitro* antimicrobial assay tests included the minimum inhibitory concentration (MIC) and the kill-time assay tests. The MIC was determined by the broth dilution method as described by National Committee for Clinical Laboratory Standards (NCCLS) (*19*). Briefly, 5 mL of Schaedler broth supplemented with hemin (10 μg/mL) and vitamin K (1 μg/mL) incorporating serial 2-fold dilution of the test compounds were inoculated with 100 μL of a 2-day-old culture of bacteria strains. They were anaerobically incubated (*P. gingivalis* ATCC 33277 and *Fusobacterium nucleatum* ATCC 10953) or aerobically incubated (*Streptococcus mutans* ATCC 25175) at 37 °C for 2 days. The MIC was recorded as the lowest concentration of the test compound to inhibit growth. The initial viable bacteria colony confirmation unit (CFU)/mL was counted. For *S. mutans*, it was 1–2 $\times$ 10^6 CFU/mL.

Kill-Time Assay Test. The kill-time curve method was used to study the bactericidal effects of MBE in a compressed mint. One piece of compressed mint was dispersed in 9.0 mL of sterile water in a sterile test tube and pre-equilibrated to 37 °C. A total of 1.0 mL of a 2-day-old culture of bacterial strains was added to the test tube containing the dispersed tablet. The tube was vortexed thoroughly and placed in a 37 °C water bath for 0.5, 2, and 5 min. At selected time intervals, a 50 μL aliquot of the mixture was removed and added to a 4.95 mL tube of broth and vortexed. The mixture was further serially diluted in sterile water and plated in Shaedler agar with hemin and vitamin K. The plates were incubated either aerobically (*S. mutans*) or anaerobically (*P. gingivalis* and *F. nucleatum*) at 37 °C for 48–72 h. After incubation, the plates were read via an automatic colony counter (IUL Countermat) or manually.

***In Vivo* Germ-Kill Test.** The *in vivo* study was a five-way, crossover design. Nine Wrigley employees (ages 25–45) in good oral and medical condition with no evidence of systemic or oral pathology participated in the study. All subjects signed a written informed consent form prior to the study. Subjects donated 1 mL of saliva at 1 h after lunch, consumed three pieces of Eclipse compressed mint containing a total of 4.2 mg of MBE or placebo mint. Subjects then donated 1 mL of saliva after consumption of mints at 30 and 60 min. For chewing gum, subjects donated 1 mL of saliva at 1 h after lunch, chewed two pieces of gum containing a total of 2 mg of MBE (or placebo gum) for 20 min and donated 1.0 mL of saliva at 40 min. For the positive control, subjects rinsed 20 mL of Listerine FreshBurst mouthwash for 30 s and donated 1 mL of saliva at 30 and 60 min. All saliva samples were collected in a sterile tube, immediately vortexed, proceeded for 10 serial dilution in sterile water, and plated in duplicate on Shaedler agar containing hemin and vitamin K. The plates were incubated in an anaerobic jar (BBL Gaspak 150) with a CO_2/H_2-generating envelope equipped by a palladium catalyst (BBL GasPak Plus) for 48 h. A dry anaerobic indicator strip was placed inside the jar to ensure a completed anaerobic condition. The total CFU was counted.

Statistical Analysis. For the kill-time assay, duplicate CFU counts were averaged and logarithm-transformed before statistical analysis. Separate analyses were performed for each organism and at each time point. Between-treatment comparisons were made using analysis of variance (ANOVA). *Posthoc* testing for the individual group difference was made by Dunnett's multiple comparison test. The [α] level was 0.05 for all tests.

For the *in vivo* germ-kill study, the mean of the logarithm CFU was tabulated for each product and at each time point. The log CFU reduction (or increment) was calculated by subtracting the post-treatment data from the baseline for each subject. Between-treatment comparisons were made by a paired *t* test performed on the log CFU reduction (or increment) at each time point.

RESULTS

1. HPLC Assay Analysis of MBE. We analyzed MBE composition by HPLC. The method showed good linearity in the concentration range between 4.05 and 162 μg/mL (R^2 = 0.999 98). For confectionery products containing MBE, we observed that the standard deviations were 1.26 and 2.32% for compressed mint and chewing gum, respectively. The MBE consisted of 94% magnolol, 1.5% honokiol, and a slight amount of essential oil. **Figure 2** shows the HPLC chromatograph of MBE.

The content and stability of MBE in chewing gum and mints were evaluated by the HPLC method as well. **Figure 3** shows the MBE content in gum and mints. Both products were stored under accelerated condition for 3 months. We observed a very stable MBE assay and compatibility with flavors and other ingredients in gum and mints.

Figure 4 shows the release of MBE from chewing gum. It is apparent that MBE did not release appreciably from gum when formulated in the center. This is due to the strong hydrophobic nature (*20*). MBE released over 50% when formulated in the

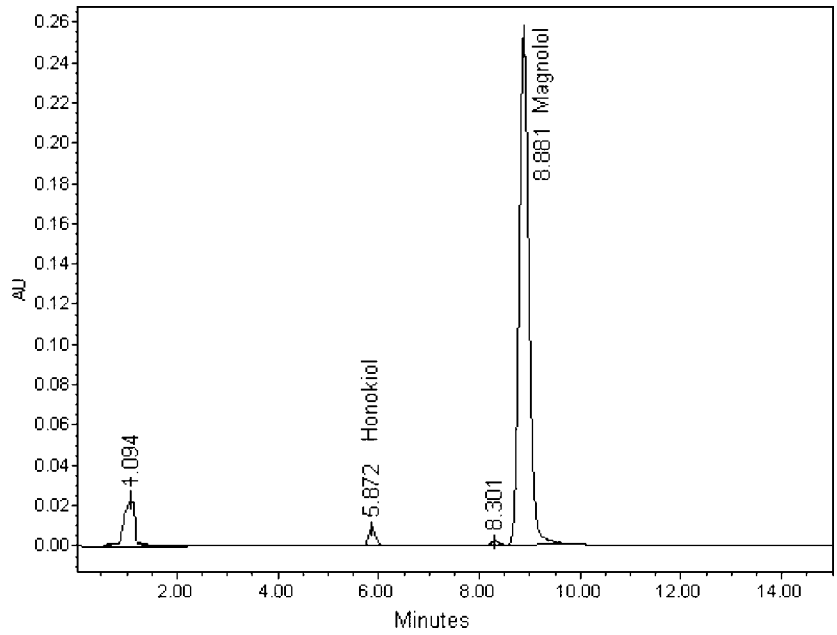

Figure 2. HPLC chromatograph of MBE.

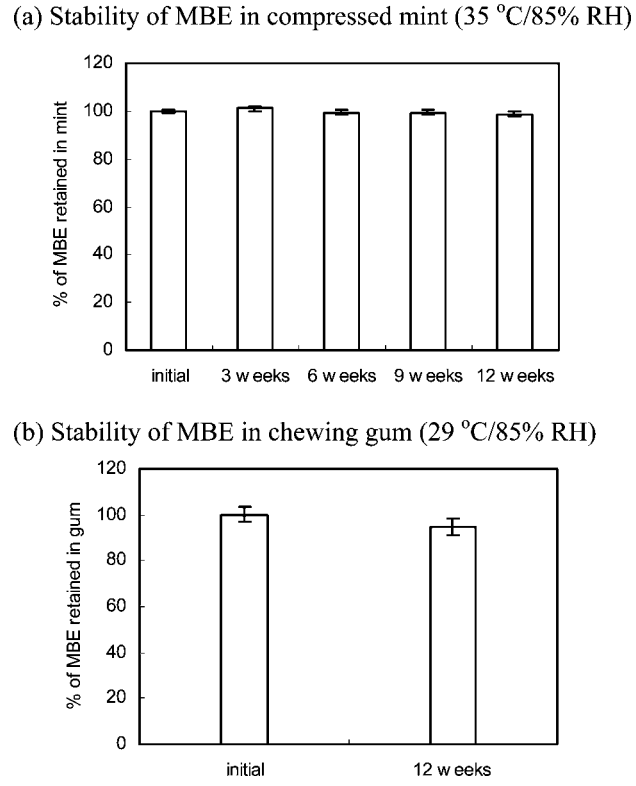

Figure 3. MBE stability analyzed by HPLC after storage under an accelerated condition: (a) compressed mint and (b) chewing gum.

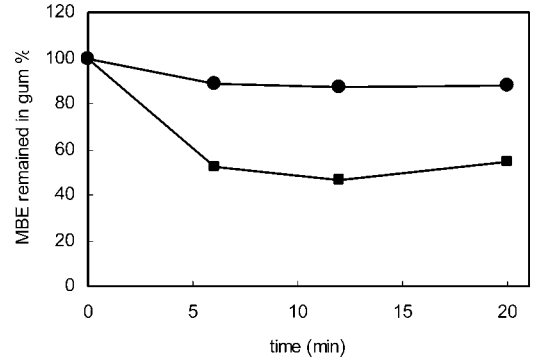

Figure 4. Release of MBE from chewing gum measured by HPLC: (●) MBE formulated in the gum center and (■) MBE formulated in the gum coating layer.

Table 1. Minimum Inhibitory Concentrations of MBE (μg/mL)

	P. gingivalis	*F. nucleatum*	*S. mutans*
MBE	8	31	16
magnolol	16	31	31
honokiol	8	16	16
peppermint oil	62.5	1000	1000
thymol		125	250
chlorhexidine gluconate	8	8	2

coating layer. The remaining was chewed back into the gum center. For this reason, we have formulated all of the MBE in the gum coating layer.

2. *In Vitro* Germ-Kill Study. MBE was found highly effective against oral microorganisms. **Table 1** lists the MIC values for MBE and the two primary components. For a comparison, the table also lists the MIC values of peppermint oil, a common flavor used in most breath-freshening products, and thymol, the active compound used by Listerine mouthwash. Chlorhexidine gluconate was used as a positive control in all studies.

Magnolol, honokiol, and the MBE showed similar germ-kill effectiveness. All of them showed significant antimicrobial activity (MIC = 16–31 μg/mL) against halitosis bacteria *P. gingivalis* and *F. nucleatum* and the cariogenic bacteria *S. mutans*. Our results on *P. gingivalis* are in agreement with an earlier study by Ho et al. (*15*), where the MIC values of magnolol and honokiol were 25 μg/mL. The MBE was more effective than peppermint oil and thymol. In a separate study, the potency of Listerine mouthwash was increased by 10-fold when thymol was replaced by an equivalent amount of MBE (i.e., 0.064%) according to the composition provided by the Listerine label (data not presented).

Figure 5 shows the kill-time assays of Extra Peppermint mint with 0.2% MBE and without MBE (placebo mint) against *F. nucleatum*, *P. gingivalis*, and *S. mutans*. The results indicated that the population was reduced by 99.9% within 2 min for the compressed mint with 0.2% of MBE for all three strains of oral

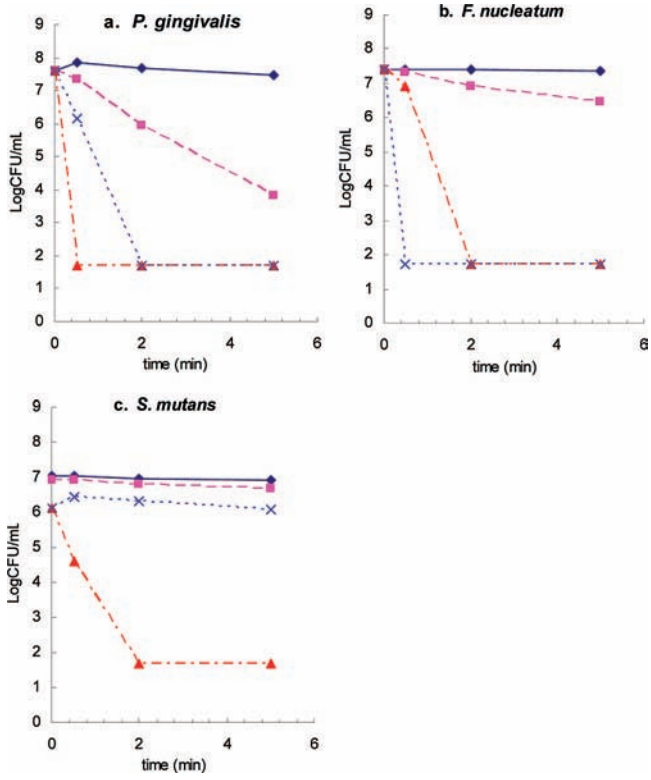

Figure 5. Kill-time assay on compressed mints against oral bacteria: (◆) flavorless mint, (■) Extra Peppermint mint, (▲) Extra Peppermint mint with 0.2% MBE, and (×) 0.12% chlorhexidine gluconate.

bacteria ($p < 0.001$). Deionized water and compressed mint without flavor, which were used as negative controls, showed no germ-kill effect. The peppermint and flavorless compressed mints were significantly less effective against oral bacteria than that of the compressed mint with 0.2% MBE and 0.12% of chlorhexidine gluconate. Compressed mint contained sorbitol, magnesium stearate, and intense sweetener. None of these ingredients showed significant germ kill, except peppermint flavor, as indicated by the flavorless compressed mint. Peppermint flavor showed some germ-kill effect against *P. gingivalis*. However, it was significantly less effective compared to MBE mint ($p < 0.001$).

3. *In Vivo* Germ-Kill Study. Unlike most clinical studies on oral malodor, which were often performed in the morning, where subjects refrained from oral hygiene and food (*3*, *4*), the *in vivo* study was performed in the afternoon to simulate the consumer's use of chewing gum and compressed mints for breath freshening. The study started from the subject at 1 h postlunch.

Figure 6 shows the testing results of the *in vivo* germ-kill study for compressed mints and chewing gum. The compressed mint with 0.2% MBE reduced total oral bacterial count by 61.6% at 30 min, and the placebo mint reduced total bacterial count by 3.6%. At 60 min, the MBE-containing mint reduced the total bacterial count by 33.8%, while the placebo mint increased total bacterial counting by 47.9%. At both time points, the MBE-containing mint demonstrated statistically significant germ-kill compared to the flavorless mint ($p < 0.05$). Bacteria reduction for the MBE-containing mint was not statistically different from Listerine FreshBurst mouthwash.

The chewing gum with 2 mg of MBE in the coating (per serving) reduced the total oral bacteria by 43.0% at 40 min, while the control gum reduced the total bacteria by 18.0%. MBE gum demonstrated a significant reduction of the total bacteria

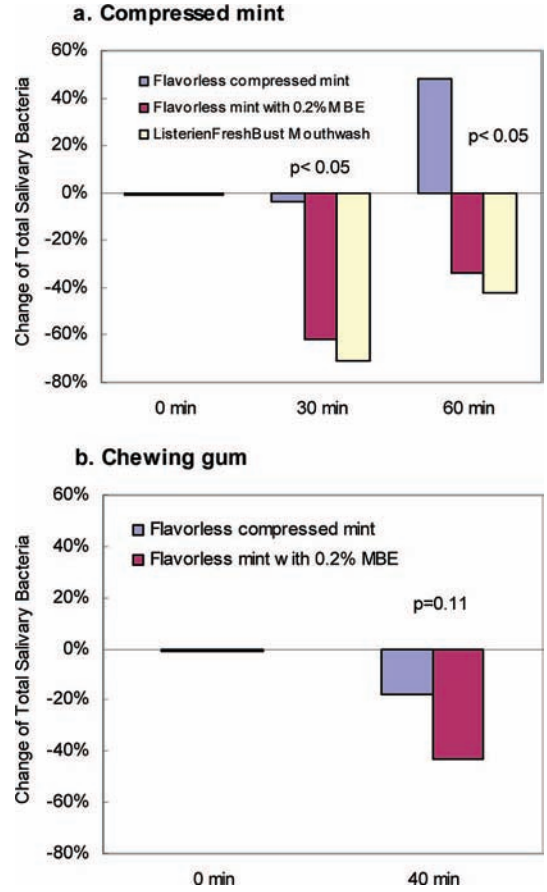

Figure 6. *In vivo* germ-kill study: (a) compressed mint and (b) chewing gum.

compared to the baseline ($p < 0.05$). Although the MBE gum did not show statistically significant germ-kill compared to Eclipse Winterfresh gum, probably because of the small number of subjects, it showed a clear trend of the germ-kill benefit for MBE-containing chewing gum compared to placebo gum.

DISCUSSION

It has been shown that, whenever oral malodor from VSC was depressed, so were the populations of oral bacteria (*2–6*, *21*, *22*). The correlation of the organoleptic score with odorigenic bacteria was investigated by several clinical studies. For example, McNamara observed that, when the bacteria-free saliva was incubated alone or added to the broth medium, no malodor was produced (*6*). However, when the organisms filtered from saliva were either added to the sterile saliva or added to the broth medium, malodor was produced. Results from these studies also indicated that Gram-positive oral bacteria produce little or no malodor. In contrast, Gram-negative oral bacteria produce pungent malodor. In our present study, the salivary bacteria were found around 10^7–10^8 microorganisms/mL. These organisms are considered to be derived from the oral surface, especially from the tongue surface. We elected to analyze salivary bacterial counts because the test provided consistent with more reliable values with a small number of subjects.

The treatment of intrinsic malodor can be achieved (1) by masking or covering malodor by flavor oils, (2) by reacting with VSC to form nonvolatile and/or odorless substances; and (3) by killing bacteria that cause the bad breath. Most breath-freshening products employed flavor oils to cover or mask malodor. Some employed zinc or copper compounds to chelate VSC. Because bacteria are the major cause of breath odor,

products containing effective germ-kill compounds will provide a long-lasting reduction of oral malodor. De Boever and Loesche demonstrated that a 1 week treatment of mouth rinse with 0.12% chlorhexidine gluconate in combination with a mechanical approach significantly reduced VSC levels by 73.3% (*21*). Rosenberg and co-workers found that a 0.2% chlorhexidine mouthwash reduced organoleptic mouth odor by 50% (*22*). Nevertheless, chlorhexidine, a synthetic antimicrobial agent, cannot be used in food because of the tooth staining effect and high toxicity. Our study indicated that MBE is a strong germ-kill agent against oral bacteria both *in vitro* and *in vivo*. MBE also showed low toxicity and fewer side effects (*16*, *17*). It may be incorporated in compressed mints and chewing gum to achieve long-lasting breath-freshening and oral-care benefits.

The kill-time assay used in this study was based on the Food and Drug Administration (FDA) tentative final monograph for oral antiseptic products (*23*). The monograph states a requirement for a reduction of 99.9% population (3 logarithm reduction) within 10 min of exposure for specific ATCC strains. Our test showed that compressed mints containing 0.2% MBE demonstrated a significant reduction of oral bacteria (>5 log) compared to the negative controls and the flavored mints ($p < 0.001$). Chewing gum and compressed mint containing MBE may provide portable oral care supplementing to dentifrice, where tooth brushing is not possible.

In our laboratory, we have evaluated a large number of natural and synthetic phenolic compounds against oral bacteria. Magnolol and honokiol are among a few of them. We have conducted a quantitative structure–activity relationship study (QSAR). By means of regression analysis of linear free-energy parameters and log(1/*C*), where *C* is the molar concentration of MIC, we have observed that the lipophilic character of the molecule or substituent as expressed by log *P* (the *n*-octanol/water partition coefficient) was the most important factor in determining the activities of the compounds examined. A good correlation of log(1/*C*) and log *P* was observed within the partition coefficient range from 1.4 to 9.5. Among them, phenol showed the lowest antimicrobial effect on *S. mutans*, while magnolol and honokiol (log $P = 5.25$) showed the highest antimicrobial effect. We plan to continue doing research in this area and publish the QSAR results in a separate paper.

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