In Vitro Screening of the Antibacterial and Anti-*Candida* Properties of Crushed Nonantimicrobial Drugs Frequently Prescribed in Nursing Homes

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**ABSTRACT**

Frail older adults often experience swallowing disorders, prompting nursing staff to crush tablets, open capsules, and mix drugs into their meals or gelled water. However, crushing drugs can lead to pharmacological and gustatory problems. As crushed drugs can stay in prolonged contact with oral microbial biofilm, the current study aimed to investigate their antimicrobial properties. Crushed drugs were diluted in 1 mL of isotonic water and assayed in vitro for: (a) growth inhibition of five bacterial strains and *Candida albicans* by the diffusion method; (b) inhibition of *Streptococcus salivarius* and *C. albicans* biofilm formation; and (c) elimination of a preformed biofilm of *S. salivarius* and *C. albicans* after 5-minute contact.

Eight of 29 crushed drugs inhibited bacterial and/or fungal growth on agar plates. Twenty-eight of 29 crushed drugs reduced the total biomass when incubated with *S. salivarius*, and 28 of 29 crushed drugs inhibited *C. albicans* biofilm formation. Preformed biomass was reduced by ≥25% by seven of 29 drugs. Crushed drugs may unbalance oral ecosystems and contribute to oral inflammation.

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Oral care for frail older adults is currently a problem for nurses and nurse’s aides in charge of oral health care (Chen, Naorungroj, Douglas, & Beck, 2013). Heavy dental plaque load is commonly observed, despite correct application of oral hygiene protocols. Several risk factors have been identified, such as oral dryness or daily use of antiseptic mouthwashes that unbalance the oral ecosystem. The current authors hypothesized that some nonantimicrobial drugs could also display antimicrobial properties when crushed and applied directly in contact with oral biofilms,
thus altering the oral ecosystem. If this hypothesis is verified, the findings would help reduce side effects of crushed medications by reinforcing current recommendations on crushing drugs.

The endogenous oral biofilm that colonizes oral surfaces is integral to good oral health, along with saliva, a healthy diet, and oral hygiene (Krom, Kidwai, & Ten Cate, 2014). Metagenomics methods have shown that the oral microbiome contains thousands of bacterial and hundreds of fungal species, as well as Archeabacteria, parasites, and viruses. However, <700 bacterial species and only a few fungal species can be grown in vitro from oral samples, whereas cultivable and uncultivable species play a role in health and disease (Diaz, Strausbaugh, & Dongari-Bagtzoglou, 2014).

An individual’s mouth harbors approximately 100 cultivable microbial strains. Conventional and DNA/RNA-based analyses are time-consuming, expensive, and wholly impractical for routine dental examination, whereas clinical examination and radiographs can immediately diagnose dental and periodontal diseases (Larsen & Fiehn, 2017; Socransky et al., 2013). However, cariogenic and periodontogenic biofilms differ from individual-to-individual and site-to-site in the same mouth, and they evolve over time.

In vitro screening experiments to assay antiseptic products or disinfection protocols are based on monospecies biofilm models. Experimental models of multispecies biofilms generally combine two to 10 cultivable bacterial and fungal species. The reason is that multispecies culture is made difficult by the fact that unlike Candidas albicans, most oral bacteria are slow-growing, nutritionally fastidious, and oxygen-sensitive. Table A (available in the online version of this article) details the prominent cultivable organisms found in the mouth (Chevalier, Ranque, & Prêcheur, 2017).

In vivo, oral microorganisms are protected by a matrix that enables specialized biofilms to colonize soft and hard surfaces in the mouth (Diaz et al., 2014). The dynamic balance between host and biofilm prevents uncontrolled microbial growth and creates a commensal protection against opportunistic pathogens (Larsen & Fiehn, 2017; Peterson et al., 2014).

Any factor able to unbalance oral ecosystems can lead to uncontrolled microbial growth, which creates a risk for oral infection (e.g., gingivitis, periodontitis), dental carries and endodontic infections, oral candidiasis, mucositis, and peri-implantitis (Peterson et al., 2014; Socransky et al., 2013). Oral infections are often complicated by pain, tooth loss, and weight loss. Microbial deposits can lead to aspiration pneumonia and blood-borne infections such as infectious endocarditis, or brain, liver, and other deep abscesses (Ewan et al., 2010).

Oral infections and the resulting inflammation also increase the risks for systemic diseases such as diabetes mellitus, rheumatoid arthritis, neurodegenerative disease (e.g., Alzheimer’s disease), atherosclerosis, cardiovascular disease, and stroke (Dietrich, Sharma, Walter, Weston, & Beck, 2013; Holtfreter et al., 2013; Otomo-Corgel, Pucher, Rethman, & Reynolds, 2012; Silva et al., 2015).

Oral hygiene aims to prevent the uncontrolled microbial growth that results in macroscopic deposits. When frail older adults cannot use a toothbrush and toothpaste, nursing staff use an oral rinse on a cotton swab or other device. However, daily use of antiseptic mouthwashes containing chlorhexidine and alcohol can induce oral candidiasis and xerostomia (Chevalier, Sakarovitch, Prêcheur, Lamure, & Pouysségur-Rougier, 2015). Consequently, crushing drugs and opening capsules could alter oral ecosystems, with xerostomia, poor access to oral care, and disability further impairing oral hygiene.

Crushing drugs is a common practice in institutional care settings, where more than 50% of residents have swallowing disorders. Swallowing disorders are behavioral conditions associated with cognitive impairment (e.g., Alzheimer’s disease), stroke, cancer, Parkinson’s disease, Sjögren’s syndrome, or certain xerostomia-inducing medications. The resulting dysphagia increases the risk of aspiration pneumonia, choking, and death (Ewan et al., 2010), whereas food and beverage refusal can lead to dehydration, anorexia, and malnutrition. As a precaution, these patients are often given blended food. Nursing home staff will often crush tablets, open capsules, and mix drugs into textured (often blended) food or gelled water—a strategy used for 28% to 33% of residents, and up to 67% of patients in geriatric hospital units (Apolo Carvajal et al., 2016; Clauson, Rull, Thibault, Ordekyan, & Tavernier, 2016; Sura, Madhavan, Carnaby, & Crary, 2012).

Listings of “safe-to-crush” drugs and consensus guidelines for their administration have been published by several groups of experts (Institute for Safe Medication Practices, 2015). For instance, in a listing of the 30 most prescribed drugs in a group of nursing homes, approximately one half of the tablets and capsules were listed “safe for crushing,” including paracetamol (acetaminophen), furosemide, memantine, zopiclone, alprazolam, oxazepam, donepezil, clopidogrel, ramipril, folic acid, amiodarone, citalopram, fluindione, digoxin, and galantamine. Conversely, aspirin, potassium chloride, amlodipine, ris-
peridone, mianserin, calcium carbonate, cholecalciferol, calcium carbonate/cholecalciferol benserazide/levodopa, rivastigmine, trinitrine, esomeprazole, and domperidone were not safe for crushing (Institute for Safe Medication Practices, 2015).

The guidance on crushing drugs states that physicians should limit drug prescription, pharmacists should propose alternative formulations such as oral drops whenever possible, and nurses should crush only drugs cleared as crushable. Medications should be crushed separately just before administration, and mixed into separate food servings. However, despite these recommendations, it is still common practice for “do not crush” medications to be given crushed, or given crushed together with other drugs and co-administered in the same food serving (Apolo Carvajal et al., 2016; Clauson et al., 2016).

Crushing drugs and opening capsules can lead to chemical (e.g., oxidation, acid–base interactions) and pharmacological (e.g., gastro-resistant or extended-release tablets) problems. The taste of some drugs, such as docusate, zopiclone, clopidogrel, and paracetamol, may be unbearable when crushed and mixed into food, and the experience is even worse when these medications are crushed and mixed all together (Lamure et al., 2015). The unbearable bitter taste of some crushed drugs could lead to food refusals and ultimately contribute to anorexia in frail older adults (Institute for Safe Medication Practices, 2015; Lamure et al., 2015).

Some drugs have known antimicrobial effects, such as aspirin and ibuprofen (Akhter, Baqai, & Aziz, 2010; Laudy, Mrowka, Krajewska, & Tyski, 2016; Ogundeji, Pohl, & Sebolai, 2016; Rusu, Radu-Popescu, Pelinescu, & Vassu, 2015) and amloidipine (Dutta, Mazumdar, DasGupta, & Dastidar, 2009; Gupta, Chanda, Rai, Kataria, & Kumar, 2016). Crushing drugs exposes the oral microbial biofilm to prolonged contact, especially in patients that have swallowing disorders and xerostomia. The question of whether some crushed drugs, in addition to chemical interactions and taste alterations, could also have intrinsic antimicrobial properties and alter the protective microbial biofilm in the mouth remains unanswered. To address this gap, the aim of the current study was to screen in vitro the antimicrobial properties and alter the protective microbial biofilm.

METHOD

Mandatory health and safety procedures were complied within the course of performing all experimental work.

Crushed Drugs

The 30 drugs tested were selected as the top drugs prescribed in 2013 in 290 nursing homes (Table B, available in the online version of this article). The drugs were obtained from the university hospital pharmacy at the lowest dosage available. Tablets were crushed manually with a mortar and pestle. The crushed tablets, opened capsules, and powders were diluted in 1 mL of isotonic water and pH-tested before performing microbial assays.

Microbial Growth Inhibition on Agar Plates

The microbial assay methods used are described in Chevalier, Médioni, and Précheur (2012). Briefly, drugs’ antibacterial properties were tested using five bacterial reference strains: Escherichia coli CIP 54.127, Staphylococcus aureus CIP 53.154, Pseudomonas aeruginosa CIP A22, and two oral species Streptococcus salivarius CIP 102.505 and Gemella haemolysans CIP 101.126. A fungal reference strain of Candida albicans ATCC 10231 was also tested.

Microbial growth inhibition was investigated by the diffusion method with 100 μL of bacterial (10⁶ colony forming unit [cfu]) or fungal (10⁶ cfu) inoculum smeared on agar plates, and 40 μL of drug solution deposited into 5-mm diameter wells. Diameter of growth inhibition zone was measured after 24 or 48 hours of incubation at 37°C. The variable was the diameter of inhibition zone around the wells in the agar plates, and results were expressed in mm (Figure A, available in the online version of this article).

E. coli, S. aureus, and P. aeruginosa are not regular members of oral microbiome (Table A). However, E. coli, S. aureus, P. aeruginosa, and C. albicans were specifically tested as these four strains are recommended by the French National Standardization Agency (Agence Française de Normalisation, 2010) as reference strains for testing antimicrobial compounds.

The preliminary panel was completed by adding two oral species, S. salivarius and G. haemolysans, as they are commonly isolated from saliva and oral biofilm samples in health and disease (Table A). These two oral species have complex nutritive needs, including iron, and are grown on agar supplemented with 5% sheep blood. Their enzymatic machinery causes lysis of red cell membrane and iron binding.

Effect of Drugs on the Formation of S. salivarius and C. albicans Biofilms

S. salivarius and C. albicans biofilms were grown on commercially available pre-sterilized, polystyrene, flat-bottomed 96-well microtiter plates. Biofilms were formed
by pipetting 100 μL of cell suspensions into the wells: suspensions contained 10⁶ S. salivarius cells in Schaedler broth or 10⁶ C. albicans cells mL⁻¹ in Roswell Park Memorial Institute (RPMI) 1640 medium buffered with 3–(N-morpholino)-propanesulfonic acid (MOPS).

Effect of Crushed Drugs on Biofilm Formation. To determine whether drugs had an effect on biofilm formation, 50 μL of each crushed drug solution was added to the wells. Isotonic water was used as a negative control. As a positive control, a mouthwash containing chlorhexidine gluconate (0.5% v/v), chlorobutanol hemihydrate (0.5% w/v), levomenthol, and ethanol (Eludril®) was selected. Chlorhexidine is a disinfectant and antiseptic agent effective against a range of bacteria, viruses, bacterial spores, and fungi. In vivo, chlorhexidine prevents the formation of dental plaque. Chlorobutanol is also an antiseptic agent that kills bacteria and fungi (Ossio & Kanani, 2013).

Plates were incubated for 48 hours (S. salivarius) or 24 hours (C. albicans) at 37°C on an orbital shaker at 100 rpm. After biofilm formation, the medium was aspirated, and nonadherent cells were removed by thoroughly washing the biofilms twice with phosphate buffer saline (PBS, pH 7.2).

For S. salivarius, the quantification of biofilm total biomass was performed by crystal violet staining. Briefly, the wells were added with 150 μL of crystal violet (1% w/v) and incubated for 15 minutes at 37°C. The plates were washed again and air-dried, then added with 200 μL of 95% ethanol and shaken for 5 minutes to suspend intracellular-bound crystal violet before measuring optical density (OD) at 630 nm. The variable was OD (unitless) of bacterial culture in the violet-colored microtiter plate wells (Figure A).

For C. albicans, a semi-quantitative measure of biofilm formation was obtained using the XTT reduction assay. The variable was OD of fungal culture in the orange-colored microtiter plate wells (Figure A).

Effect of Crushed Drugs on Preformed Biofilms. To determine whether drugs had an effect on a preformed biofilm, S. salivarius and C. albicans biofilms were obtained as described above. After incubation for 48 hours (S. salivarius) or 24 hours (C. albicans) at 37°C, the growth medium was aspirated, nonadherent cells were removed by thoroughly washing the biofilms with PBS, and 100 μL of crushed drug solution was added to the wells. Plates were incubated for 5 minutes on an orbital shaker at 100 rpm. For this experiment, the protocol described by Chevalier et al. (2012) was re-adapted to test plant extracts for crushed drugs. Preformed biofilms were incubated for 5 minutes instead of 2 hours to mimic a real-world situation with frail older adults with swallowing disorders. After washing the biofilms, the crystal violet or XTT reactions were measured to evaluate the biomass or reduction of cell viability in a preformed biofilm.

RESULTS
Medications and pH Measures

The 30 drugs most often prescribed in nursing homes and studied herein are listed in Table B, along with their formulae, formulations, main indications, pH, and safe-to-crush/do-not-crush status.

The most frequently prescribed drug was paracetamol, followed in decreasing order by aspirin, furosemide, levothyroxine, memantine, potassium chloride, zopiclone, amiodipine, alprazolam, oxazepam, risperidone, mianserin, donepezil, macrogol 4000, clopidogrel, calcium carbonate/cholecalciferol, benserazide/levodopa, ramipril, folic acid, amiodarone, rivastigmine, glycerol, citalopram, fluindione, digoxin, trinitrine, esomeprazole, galantamine, cholecalciferol, and domperidone.

Glycerol suppository was excluded from microbial assays. Aspirin and benserazide/levodopa in powder form were tested because severe cases of swallowing disorders carry a risk of choking when drinking water, so patients are given gelled water instead, in which case powder may be administered in the gelled water, similarly to crushed tablets and opened capsules.

For the 29 drugs tested, pH in solution ranged from 5 (clopidogrel and fluindione) to 8.5 (macrogol 4000 and calcium carbonate/cholecalciferol). pH < 6 favors the development of dental caries (Chevalier, Ranque, & Prêcheur, 2017; Larsen & Fiehn, 2017). Clopidogrel and fluindione were the only drugs with an acidic pH < 6.

Microbial Growth Inhibition

All assays were performed in triplicate. Eight of 29 drugs inhibited bacterial and/or fungal growth on agar plates (Table, Figure A, and Table C [available in the online version of this article]).

In addition to antimicrobial properties, hemolytic properties were screened by measuring diameter of hemolysis on 5% sheep blood agar plates. Results, in decreasing order, were: galantamine, 26 mm (SD = 1.4 mm); benserazide/levodopa, 17.5 mm (SD = 3.5 mm); clopidogrel, 12.5 mm (SD = 2.1 mm); amiodipine, 11 mm; alprazolam, 9.5 mm (SD = 0.7 mm); citalopram, 8 mm (SD = 2.8 mm); domperidone, 8 mm; mianserin, 7 mm; amiodarone, 6 mm; and potassium chloride, 6 mm. Among these 10 active
ingredients, three (i.e., amiodarone, domperidone, potassium chloride) displayed hemolytic activity but no inhibition of bacterial or fungal growth.

**Streptococcus salivarius** Biofilm

All drugs tested, except clopidogrel, reduced the biofilm total biomass when they were incubated with *S. salivarius* during biofilm formation ([Figure 1](#) and [Figure B](#) [available in the online version of this article]). These drugs were at least as efficient at reducing biomass as the chlorhexidine mouthwash that served as antimicrobial reference (36.4% [SD = 0.5%] residual biomass compared to 100% control untreated biofilm).

After 5 minutes of contact exposure of a 24-hour preformed biofilm to chlorhexidine mouthwash, 69.2% (SD = 4.3%) residual biofilm was observed. Six drugs were able to reduce the bacterial biomass by ≥25% (i.e., paracetamol, aspirin, amlodipine, alprazolam, risperidone, and rivastigmine; [Figure 1](#) and [Figure C](#) [available in the online version of this article]). In both experiments, during biofilm formation or with a preformed biofilm, none of the drugs tested increased bacterial growth or biofilm formation: values >100% resulted from drug–dye (crystal violet) interactions.

**Candida albicans** Biofilm

All drugs tested, except macrogol, reduced fungal cell viability when incubated with *C. albicans* during biofilm formation ([Figure 2](#) and [Figure D](#) [available in the online version of this article]). Three drugs were as efficient as the chlorhexidine mouthwash and totally inhibited *C. albicans* growth (i.e., aspirin, amlodipine, and alprazolam). Twelve additional drugs reduced *Candida* viability by ≥75%, in decreasing order of efficacy: memantine, potassium chloride, paracetamol, cholecalciferol, donepezil, amiodarone, fluindione, levothyroxine, oxazepam, furosemide, esomeprazole, and risperidone.

The chlorhexidine mouthwash efficiently reduced the 24-hour preformed *C. albicans* biofilm. After 5 minutes of contact, there was only 4.2% (SD = 0.5%) residual biofilm.

### TABLE

<table>
<thead>
<tr>
<th>Drug</th>
<th><em>Escherichia coli</em> CIP 54.127</th>
<th><em>Pseudomonas aeruginosa</em> CIP A22</th>
<th><em>Staphylococcus aureus</em> CIP 53.154</th>
<th><em>Gemella haemolysans</em> CIP 101.126</th>
<th><em>Streptococcus salivarius</em> CIP 102.505</th>
<th><em>Candida albicans</em> ATCC 10231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>14.5 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>13.5 (0.7)</td>
<td>8.75 (0.3)</td>
<td>18 (4.2)</td>
<td>23 (5.6)</td>
<td>13.5 (0.7)</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0</td>
<td>0</td>
<td>10 (1.4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Drugs inhibited microbial growth by the diffusion method. Drugs are listed by decreasing order of prescription. Crushed tablets (alprazolam), opened capsules (amlodipine), and powders (aspirin) were diluted in 1 mL of isotonic water, and 40 μL of the drug solutions were deposited in pits in agar plates.
in the wells. Only one drug, amlodipine, was able to reduce the bacterial biomass by approximately 25% (Figure 2 and Figure E [available in the online version of this article]). In both experiments, none of the drugs tested increased fungal growth or biofilm formation: values >100% resulted from drug–dye (orange XTT) interactions.

**DISCUSSION**

To the current authors' knowledge, this is the first study to show that some crushed drugs have antimicrobial properties in vitro and could contribute to altered oral biofilm and thus increase risk of oral infections.

Some drugs also displayed hemolytic properties at the concentrations tested. This result was not anticipated, but must be considered, because occult bleeding is frequent in the mouth due to gingival inflammation during gingivitis and periodontitis (Otomo-Corgel et al., 2012). This unexpected result suggests that some drugs could induce red cell lysis, providing iron and other nutrients to fastidious oral germs, and thus contribute to unbalanced oral biofilm.

The 29 most prescribed drugs in nursing homes were screened and evaluated according to whether they were safe to crush or listed as “do not crush” (Institute for Safe Medication Practices, 2015), because in practice, nursing home staff do not always follow the guidance on crushing (Apolo Carvajal et al., 2016; Clauson et al., 2015; Sura et al., 2012). Further investigations are needed to test more crushed drugs, alone and in combination. Polymicrobial bacterial–fungal biofilms should also be tested, despite the fact that highly complex oral biofilms cannot be modeled in vitro (Diaz et al., 2014; Lauritano et al., 2016).

The study was a preliminary screening and did not intend to test the effect of crushed drugs on mixed fungal–bacterial biofilms. Only two model monospecies biofilms grown with *S. salivarius* and *C. albicans* were tested, but this approach was sufficient to observe in vitro antimicrobial properties of the 29 drugs tested.

This was an observational study, without statistical analysis, as the authors did not intend to reduce any one given organism because abscessed teeth and periodontal infections are always treated with presumptive antibiotic treatment, which is not targeted against a specific bacterial species but against the faster-growing whole microbial population. The key finding of the current study is that crushed medications may unbalance oral ecosystems.

**Antimicrobial properties of crushed drugs against dental plaque, respiratory pathogens, or *C. albicans* could appear as a positive side effect for frail older adults (Ortega et al., 2015).** However, the current study demonstrated that crushing drugs and opening capsules could alter oral ecosystems. These results could also apply to drug excre-
tion in saliva and explain why a strong association exists between xerostomia and medications of any given pharmacotherapy family (Nederfors, Isaksson, Mornstad, & Dahlöf, 1997).

Crushing may also induce local allergic contact, burns, or injuries to oral mucosa, especially with aspirin and other drugs such as clopidogrel or fluindione, which have a low pH after crushing (pH 5). Acidity favors dental caries and *C. albicans* outgrowth (Koopman et al., 2015). Furthermore, crushing drugs and opening capsules may also induce allergies among nurses who prepare medications and mix them into food or gelled water (Akhter et al., 2010; Laudy et al., 2016; Ogundeji et al., 2016).

No chemical similarities to antibiotic or antifungal agents were found in the current study (Table B); however, antibacterial and/or antifungal properties of aspirin, amlodipine, and benserazide/levodopa have previously been described in vitro (Akhter et al., 2010; Kruszewska, Zaręba, & Tyski, 2012). Amlodipine, mianserin, and citablopram may also have antiparasitic properties. Review of the literature failed to find other antimicrobial properties attributed to the drugs tested in the current study, or to their excipients.

Aspirin inhibits the growth of many Gram-negative and Gram-positive bacteria (Akhter et al., 2010; Demirag, Esen, Zivalioglu, Leblebicioglu, & Keceligil, 2007). Aspirin can alter the production of *S. aureus* capsular polysaccharides, unmasking surface adhesions and increasing their capacity to invade epithelial cells (Alvarez et al., 2010), which could facilitate the persistence of *S. aureus* in the oral cavity (Ortega et al., 2015). Aspirin also inhibits the growth of *Candida* spp. and *Cryptococcus* spp. (Farrugia, Bannister, Vassallo, & Balzan, 2013; Ogundeji et al., 2016; Rosato et al., 2016; Rusu et al., 2015; Yang, Liao, Cong, Lu, & Yang, 2016). Aspirin could increase antifungal susceptibility in *Candida* spp. (Rosato et al., 2016) and decrease antibiotic susceptibility in some bacterial species (Laudy et al., 2016).

Amlodipine is an inhibitor of voltage-gated Ca**2+** channels in mammals and parasites, and can inhibit the growth of *S. aureus, E. coli, P. aeruginosa* (Kruszewska et al., 2012), *Listeria monocytogenes* (Dutta et al., 2009), *C. albicans*, and *Candida glabrata* (Gupta et al., 2016). Benserazide can inhibit the growth of *Prevotella* spp. (Wang, McKain, Walker, & Wallace, 2004), and benserazide/levodopa could have some antibacterial properties in vitro, especially against *S. aureus* (Kruszewska et al., 2012).

Parasites such as *Entamoeba gingivalis* or *Trichomonas tenax* can often colonize deep periodontal pockets (Lauritano et al., 2016). Amlodipine can inhibit the growth of *Acanthamoeba* spp. (Baig, Iqbal, & Khan, 2013), *Leishmania* spp., and *Trypanosoma cruzi* (Reimao, Scotti, & Tempone, 2010). Mianserin kills *Leishmania donovani* by depleting ergosterol levels (Dinesh, Kaur, Swamy, & Singh, 2014). However, the putative impact of crushed amlodipine or mianserin against oral parasites is unknown.

**CONCLUSION**

In addition to creating pharmacological problems and potentially inducing anorexia, many crushed medications could unbalance oral ecosystems, and thus contribute to the development of uncontrolled microbial deposits in the mouth, increasing risks for oral inflammation, oral pain, oral infections, and aspiration pneumonia among frail older adults. Based on the current study results, there is a risk with virtually all drugs tested, with each drug displaying a specific antimicrobial profile according to the microorganisms tested. However, caregivers of patients with swallowing problems or cognitive disorders may have no other alternative to crushing their medications. Pharmaceutical companies could be urged to develop specific “older adult–friendly” medicines in line with “child-friendly” medicines in an effort to minimize the risks of crushing medications.

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Antibacterial and Anti-Candida Properties of Crushed Drugs


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Table A. Key characteristics of oral biofilms and examples of common cultivable species isolated from oral biofilms in vivo (Ewan et al., 2010; Socransky et al., 2013; Diaz, Strausbaugh & Dongari-Bagtzoglou, 2014; Chevalier, Ranque & Prêcheur, 2017)

Healthy oral biofilm

Oral streptococci are early tooth colonizers, via specific attachment to the salivary pellicle composed of host-derived proteins and glycoproteins. Their main nutrients are saliva and dietary sugars.


Cariogenic biofilm

*Streptococcus, Actinomyces* and *Lactobacillus* spp. are cariogenic. *S. mutans* has the most active virulence factors:

1) Phosphoenolpyruvate system: quick utilization of any trace of sugar in the environment.

2) Glycolytic system (glycosyl hydrolases): acid production and enamel-dentin lysis, via
   - The homofermentative pathway, activated by exogenous sugars and anaerobic conditions (thick dental plaque or cavities). Yields >80% lactic acid residues from glucose, lowering pH to under 5.5.
   - The heterofermentative pathway, less aggressive for tooth, activated by aerobic conditions, sugar shortage or alkaline pH. Yields lactic, acetic, butyric, propionic and formic acids.

3) Survives in an acidic environment.

4) Polysaccharides (synthesized by glycosyltranferases): intracellular polysaccharides as energetic stores (*S. mutans, Actinomyces* spp.), and soluble and insoluble extracellular polysaccharides, called glucans (*Streptococcus* sp., *Lactobacillus* spp.). Glucans contribute to matrix structure, adherence to hard surfaces, and bacterial coaggregation.

Mature biofilm contains gram-negative anaerobes and, once infected, the pulp necrotizes.


Periodontal biofilm

Oral streptococci and *Veillonella* spp. are among the early gingival colonizers, via adhesion to host receptors on epithelial cells. Their primary nutrient is the serum exudate in the gingival sulcus. *Fusobacterium nucleatum* is a key intermediate specialized in intermicrobial coaggregation. The mature biofilm is characterized by complex
metabolic exchanges and shifts from cocc to rod-shaped species, oxygen-tolerant species to strict anaerobes, non-motile to motile species, and gram-positive to gram-negative species. Important species are *Porphyromonas*, *Prevotella*, *Tannerella* and *Treponema* spp. *Aggregatibacter actinomycetemcomitans* specifically triggers host inflammation. The matrix contains extracellular DNA released after cellular lysis (biofilm stabilization, energy, new genetic information).

**Common species:** caries-associated species and *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella* spp. (*P. intermedia, P. nigrescens*), *Tannerella* spp. (*T. denticola, T. forsythia*)

**Candida albicans biofilm**

*C. albicans* can switch from yeast-like round cells to filamentous/hyphal cells. Adherence to mucosa occurs via cell-surface hydrophobicity and glycoproteins (ALS: agglutinin-like sequence; HWP1: hyphal wall protein 1). Hyphae have increased resistance against phagocytosis, enhanced adherence to host surfaces, a scaffolding role in biofilms (main partner *F. nucleatum*), and the ability to invade epithelium resulting in tissue damage. Secreted aspartyl proteinases (SAP) and phospholipases contribute to salivary glycoprotein breakdown and mucosal invasion.

**Common species:** oral bacterial strains and *Candida* spp. (*C. albicans, C. glabrata, C. krusei*).

**Critical oral biofilm (COB)**

This late stage of uncontrolled oral biofilm can contain any oral species and non-oral respiratory and digestive pathogens: *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*.

**Common species:** oral bacterial strains and *Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus* and/or *Streptococcus pneumoniae*. 
Table B. The 30 most prescribed drugs in nursing homes, in descending order, and pH after dilution in 1 mL of isotonic water

<table>
<thead>
<tr>
<th>Drug INN (Laboratory)</th>
<th>Formula</th>
<th>Formulation</th>
<th>Main indication</th>
<th>pH in isotonic water</th>
<th>Safe to crush*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paracetamol</strong></td>
<td><img src="image" alt="Paracetamol" /></td>
<td>Capsule 500 mg</td>
<td>Analgesic</td>
<td>7.5</td>
<td>Crushable</td>
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<td>(or acetaminophen)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Aspirin</strong></td>
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<td>Powder 100 mg</td>
<td>Analgesic, antiplatelet</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>(or acetylsalicylic acid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Furosemide</strong></td>
<td><img src="image" alt="Furosemide" /></td>
<td>Tablet 20 mg</td>
<td>Antihypertensive, loop diuretic</td>
<td>6</td>
<td>Crushable</td>
</tr>
<tr>
<td>(Sanofi-Aventis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Levothyroxine</strong></td>
<td><img src="image" alt="Levothyroxine" /></td>
<td>Tablet 25 µg</td>
<td>Thyroid hormone deficiency</td>
<td>6</td>
<td>Crushable</td>
</tr>
<tr>
<td>(Merck)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Memantine</strong></td>
<td><img src="image" alt="Memantine" /></td>
<td>Tablet 10 mg</td>
<td>Alzheimer’s disease</td>
<td>6</td>
<td>Crushable</td>
</tr>
<tr>
<td>(Lundbeck)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Potassium chloride</strong></td>
<td>K-Cl</td>
<td>Capsule 600 mg</td>
<td>Hypokalemia</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>(UCB Pharma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Company</td>
<td>Formulation</td>
<td>Strength/Property</td>
<td>S mour</td>
<td>Crushable</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------------------------------------------</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>Zopiclone (Arrow)</td>
<td></td>
<td>Tablet</td>
<td>7.5 mg Benzodiazepine-like hypnotic</td>
<td>6.5</td>
<td>Crushable</td>
</tr>
<tr>
<td>Amlodipine (Pfizer)</td>
<td></td>
<td>Capsule</td>
<td>5 mg Antihypertensive, calcium channel blocker</td>
<td>6.5</td>
<td>No</td>
</tr>
<tr>
<td>Alprazolam (Mylan)</td>
<td></td>
<td>Tablet</td>
<td>0.25 mg Anxiolytic, benzodiazepine</td>
<td>6.5</td>
<td>Crushable</td>
</tr>
<tr>
<td>Oxazepam (Biodim)</td>
<td></td>
<td>Tablet</td>
<td>10 mg Anxiolytic, benzodiazepine</td>
<td>6</td>
<td>Crushable</td>
</tr>
<tr>
<td>Risperidone (Janssen Cilag)</td>
<td></td>
<td>Tablet</td>
<td>1 mg Neuroleptic</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Mianserin (Arrow)</td>
<td></td>
<td>Tablet</td>
<td>10 mg Tetracyclic antidepressant</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Type</td>
<td>Formulation</td>
<td>Dosage</td>
<td>Indication</td>
<td>Score</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>-----------------------------------</td>
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</tr>
<tr>
<td>Donepezil (Mylan)</td>
<td>Tablet</td>
<td>5 mg</td>
<td></td>
<td>Acetylcholinesterase inhibitor,</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alzheimer’s disease</td>
<td></td>
</tr>
<tr>
<td>Macrogol 4000 (Bayer)</td>
<td>Powder</td>
<td>5.9 g</td>
<td></td>
<td>Laxative</td>
<td>8.5</td>
</tr>
<tr>
<td>Clopidogrel (Sanofi Pharma)</td>
<td>Tablet</td>
<td>75 mg</td>
<td></td>
<td>Anti-platelet</td>
<td>5</td>
</tr>
<tr>
<td>Calcium carbonate, cholecalciferol (or vitamin D3) (Sandoz)</td>
<td>Tablet</td>
<td>100 mg</td>
<td></td>
<td>Osteoporosis</td>
<td>8.5</td>
</tr>
<tr>
<td>Benserazide/Levodopa (or co-beneldopa) (Roche)</td>
<td>Powder</td>
<td>50 mg / 12.5 mg</td>
<td></td>
<td>Parkinson’s disease</td>
<td>6.5</td>
</tr>
<tr>
<td>Ramipril (Sanofi-Aventis)</td>
<td>Tablet</td>
<td>1.25 mg</td>
<td></td>
<td>Antihypertensive, angiotensin-</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>converting-enzyme inhibitor</td>
<td></td>
</tr>
<tr>
<td>Folic acid (CCD)</td>
<td>Tablet</td>
<td>5 mg</td>
<td></td>
<td>Vitamin B0</td>
<td>6</td>
</tr>
<tr>
<td><strong>Amiodarone (Arrow)</strong></td>
<td>Tablet 200 mg</td>
<td>Antiarrhythmic agent</td>
<td>6.5</td>
<td>Crushable</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------</td>
<td>----------------------</td>
<td>-----</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td><strong>Rivastigmine (Novartis)</strong></td>
<td>Capsule 1.5 mg</td>
<td>Alzheimer’s disease, cholinergic agent</td>
<td>6</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Glycerol (or E422) (Cooper)</strong></td>
<td>Suppository Lubricant</td>
<td>Not tested</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Citalopram (Lundbeck)</strong></td>
<td>Tablet 20 mg</td>
<td>Antidepressant, serotonin reuptake inhibitor</td>
<td>7.5</td>
<td>Crushable</td>
<td></td>
</tr>
<tr>
<td><strong>Fluindione (Merck Serono)</strong></td>
<td>Tablet 20 mg</td>
<td>Anticoagulant, vitamin K antagonist</td>
<td>5</td>
<td>Crushable</td>
<td></td>
</tr>
<tr>
<td><strong>Digoxin (Teofarma)</strong></td>
<td>Tablet 0.25 mg</td>
<td>Cardiac glycoside</td>
<td>6</td>
<td>Crushable</td>
<td></td>
</tr>
<tr>
<td><strong>Trinitrine (Tonipharm)</strong></td>
<td>Tablet 0.15 mg</td>
<td>Angina</td>
<td>6</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Esomeprazole (Astra Zeneca)</strong></td>
<td>Tablet 20 mg</td>
<td>Inhibits gastric acid secretion, proton pump inhibitor</td>
<td>6</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>Form</strong></td>
<td><strong>Dosage</strong></td>
<td><strong>Indication</strong></td>
<td><strong>Ref</strong></td>
<td><strong>Crushable</strong></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>------------------------------------------------------</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>Galantamine (Janssen-Cilag)</td>
<td>Capsule</td>
<td>24 mg</td>
<td>Alzheimer’s disease, acetylcholinesterase inhibitor</td>
<td>6</td>
<td>Crushable</td>
</tr>
<tr>
<td>Cholecalciferol (Crinex)</td>
<td>Single-dose vial</td>
<td>2.5 mg</td>
<td>Vitamin D3</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Domperidone (Arrow)</td>
<td>Tablet</td>
<td>10 mg</td>
<td>Nausea, dopamine D2 and D3 receptor antagonist</td>
<td>6.5</td>
<td>No</td>
</tr>
</tbody>
</table>

*Institute for Sage Medication Practices, 2015*
Figure A. Variables and their measures. Upper left - *Staphylococcus aureus* inhibited by amlodipine. A 5-mg capsule was opened and the content diluted in 1 mL of isotonic water; 40 µL of solution per pits. Serial ½ dilution and negative control (isotonic water). Lower left - Hemolytic properties of crushed amlodipine. Serial ½ dilution and negative control (isotonic water). Pure: diameter of hemolysis 11 mm around pits containing amlodipine solution (40 µL). Upper right - Crystal violet coloring of *Streptococcus salivarius* biofilm grown in microtiter plates. A darker purple color corresponds to a thicker biofilm in the pits. Lower right - XTT orange coloring of *Candida albicans* biofilm grown in microtiter plates. A darker orange color corresponds to a thicker biofilm in the pits.
Table C. Antimicrobial properties of 29 drugs commonly prescribed in nursing homes: 8 out of 29 crushed drugs inhibited microbial growth by the diffusion method, and are listed here in decreasing order of prescription. Crushed tablets (alprazolam, mianserin, clopidogrel, citalopram, fluindione), opened capsules (amlodipine) and powders (aspirin, benserazide/levodopa) were diluted in 1 mL of isotonic water, and 40 µL of drug solutions were deposited into pits in agar plates. Results are expressed as diameter of inhibition zone (mm).

<table>
<thead>
<tr>
<th></th>
<th>Escherichia coli CIP 54.127</th>
<th>Pseudomonas aeruginosa CIP A22</th>
<th>Staphylococcus aureus CIP 53.154</th>
<th>Gemella haemolysans CIP 101.126</th>
<th>Streptococcus salivarius CIP 102.505</th>
<th>Candida albicans ATCC 10231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>9 ± 0</td>
<td>14.5 ± 0.7</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>13.5 ± 0.7</td>
<td>8.75 ± 0.3</td>
<td>18 ± 4.2</td>
<td>23 ± 5.6</td>
<td>13.5 ± 0.7</td>
<td>10 ± 2.8</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>10 ± 1.4</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Mianserin</td>
<td>9.5 ± 0.7</td>
<td>0 ± 0</td>
<td>8.75 ± 1.8</td>
<td>8 ± 0</td>
<td>7 ± 0</td>
<td>8.5 ± 0.7</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 ± 0</td>
<td>9.5 ± 2.1</td>
<td>10 ± 4.2</td>
<td>6.25 ± 0.3</td>
<td>12.5 ± 2.1</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Benserazide/Levodopa</td>
<td>13.5 ± 0.7</td>
<td>18 ± 0</td>
<td>34 ± 5.6</td>
<td>34 ± 0</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
<tr>
<td>Citalopram</td>
<td>16 ± 0</td>
<td>6 ± 0</td>
<td>11 ± 0</td>
<td>12.5 ± 0.7</td>
<td>9.5 ± 0.7</td>
<td>10.5 ± 0.7</td>
</tr>
<tr>
<td>Fluindione</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
<td>16.5 ± 7.8</td>
<td>9 ± 4.2</td>
<td>0 ± 0</td>
<td>0 ± 0</td>
</tr>
</tbody>
</table>
Figure B. Anti-biofilm properties of drugs commonly prescribed in nursing homes: inhibition of the formation of *Streptococcus salivarius* biofilm grown for 48 hrs. Results are expressed as % growth compared to control. Control: 100% of *S. salivarius* biomass (crystal violet) in a biofilm grown for 48 hrs without medication.
Figure C. Anti-biofilm properties of drugs commonly prescribed in nursing homes, after 5-min contact: biomass reduction of a preformed *Streptococcus salivarius* biofilm grown for 48 hrs. Results are expressed as % biomass compared to control. Control: 100% of *S. salivarius* biomass (crystal violet) in a biofilm grown for 48 hrs without medication. Values >100% are attributed to an interaction between certain drugs and the crystal violet dye used to measure optical density.
Figure D. Anti-biofilm properties of drugs commonly prescribed in nursing homes: inhibition of the viability of *Candida albicans* in a biofilm grown for 24 hrs. Results are expressed as % viability compared to control. Control: 100% of *C. albicans* viability (XTT orange dye) in a biofilm grown for 24 hrs without medication.
Figure E. Anti-biofilm properties of drugs commonly prescribed in nursing homes, after 5-min contact: viability reduction in a preformed *Candida albicans* biofilm grown for 24 hrs. Results are expressed as % viability compared to control. Control: 100% of *C. albicans* viability (XTT orange dye) in a biofilm grown for 24 hrs without medication. Values >100% are attributed to an interaction between certain drugs and the XTT orange dye used to measure optical density.