Next Generation Chemical Preservatives:

Protecting People, Products, and our Planet

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DECEMBER 10, 2014

Preservatives are necessary in liquid products

All water-based consumer products require preservation

Preservatives prevent growth of bacteria, yeast, and mold

- Odor issues
- Product performance
- Pathogens

Image source: soapqueen.com

Conventional preservatives can be hazardous to human health and the environment

Preservatives are bioactive molecules by design

Human health risks:

- Skin and eye irritation
- Skin and respiratory sensitization
- Endocrine activity
- Cancer
- Reproductive toxicity

Environmental risks:

- Not degraded by sewage treatment
- Acute toxicity
- Bioaccumulation and bioconcentration
- Persistence

Image sources: Mayo Foundation; usresponserestoration.wordpress.com

Goal:
Recommend safer preservatives for home and personal care products

How we approached this challenge

Partner organizations

From biomimicry to industrially relevant chemicals

Evaluation of alternatives

Beyond “drop-ins” – formulation strategies

Concluding thoughts and recommendations

Partnerships with industry support actionable research

BEAUTYCOUNTER

Cosmetics

FDA-regulated

Acidic pH

Replace phenoxyethanol

SEVENTH GENERATION

Home and personal care

EPA-regulated

Basic pH

Replace isothiazolinones

Safer, effective, biodegradable alternatives

Inspiration from biology translates into functional themes

BIOMIMICRY 3.8

Membrane disruption

- Fatty acids (human skin)
- Terpenes (Douglas fir tree)
- Cationic peptides (Chungan frog skin)

Synergistic formulation

- Peptide mixture (American dog tick)
- Nonanal, indole (Reticulated giraffe)

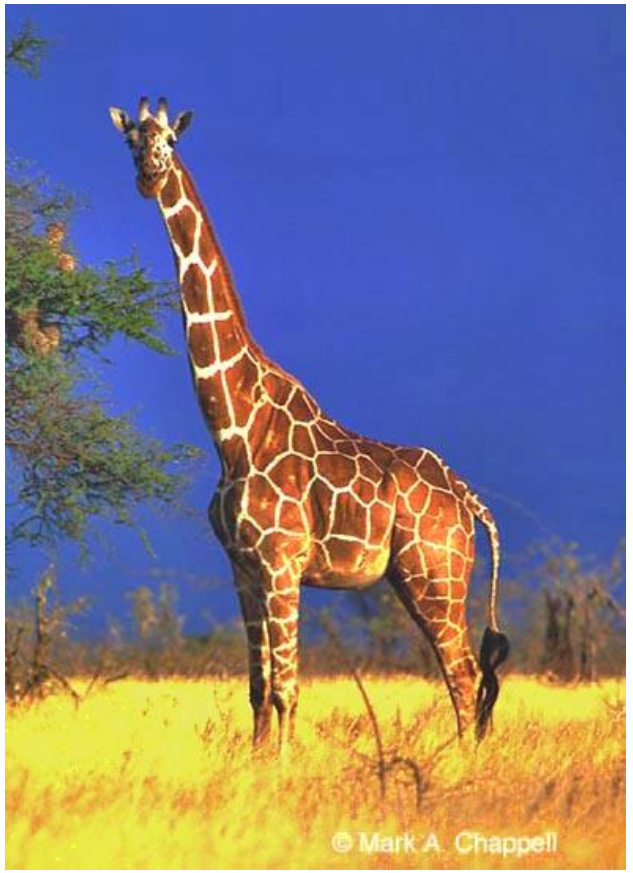
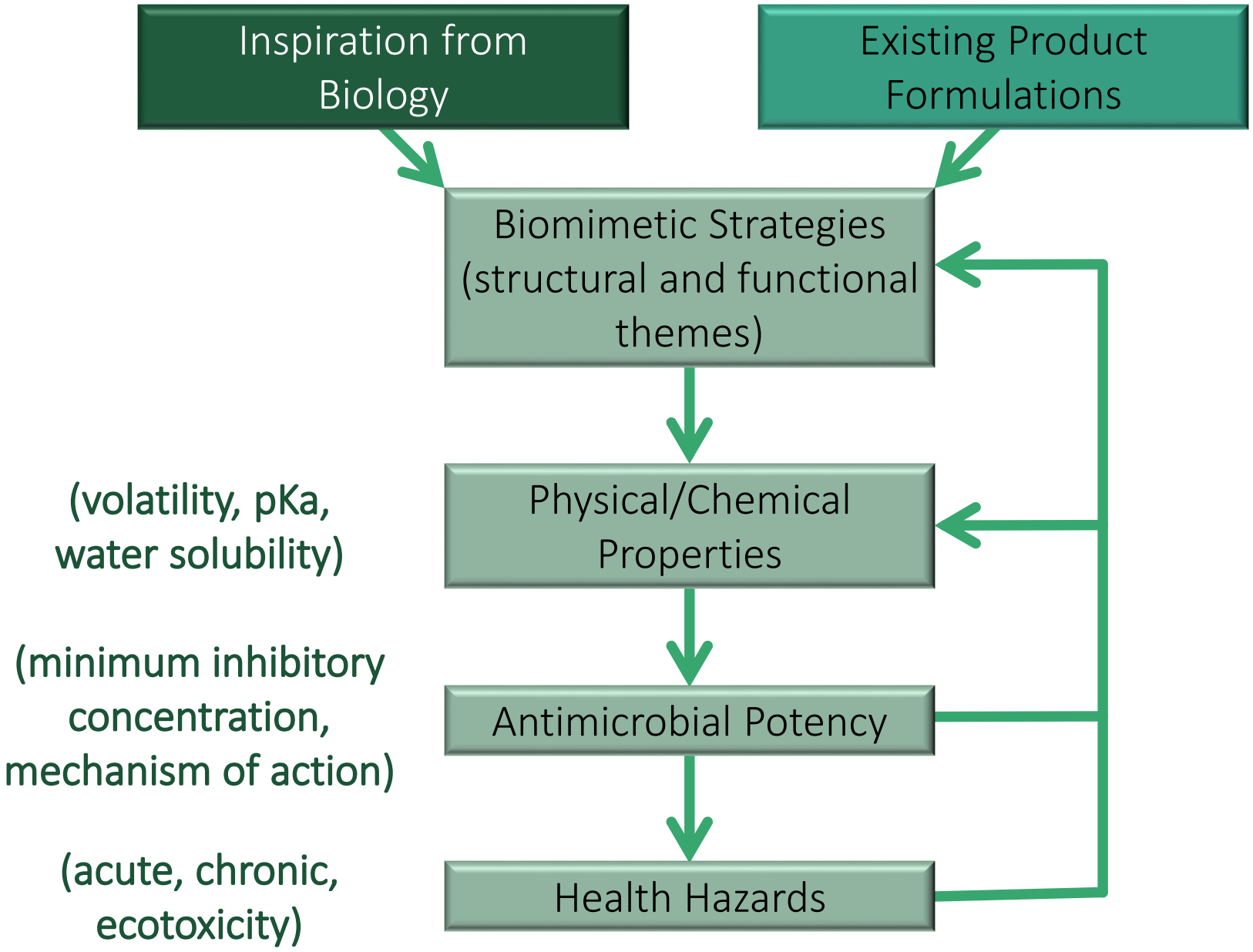


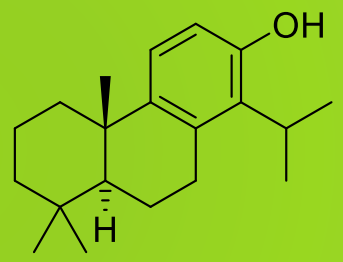
Image sources: www.faculty.ucr.edu, www.commons.wikimedia.org

Iterative evaluation…

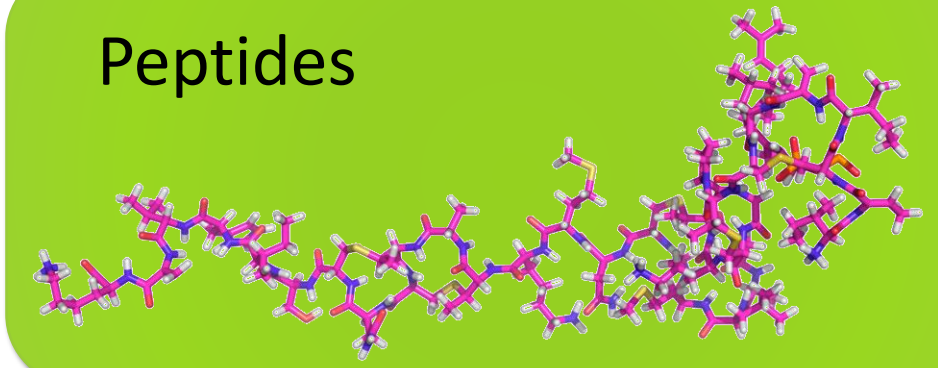


…takes us from biology to biomimetic design

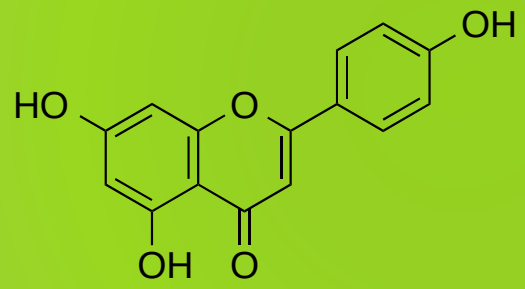
Terpenes



Peptides



Flavonoids



Fatty Acids

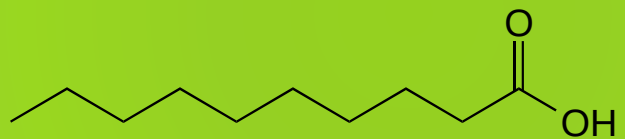
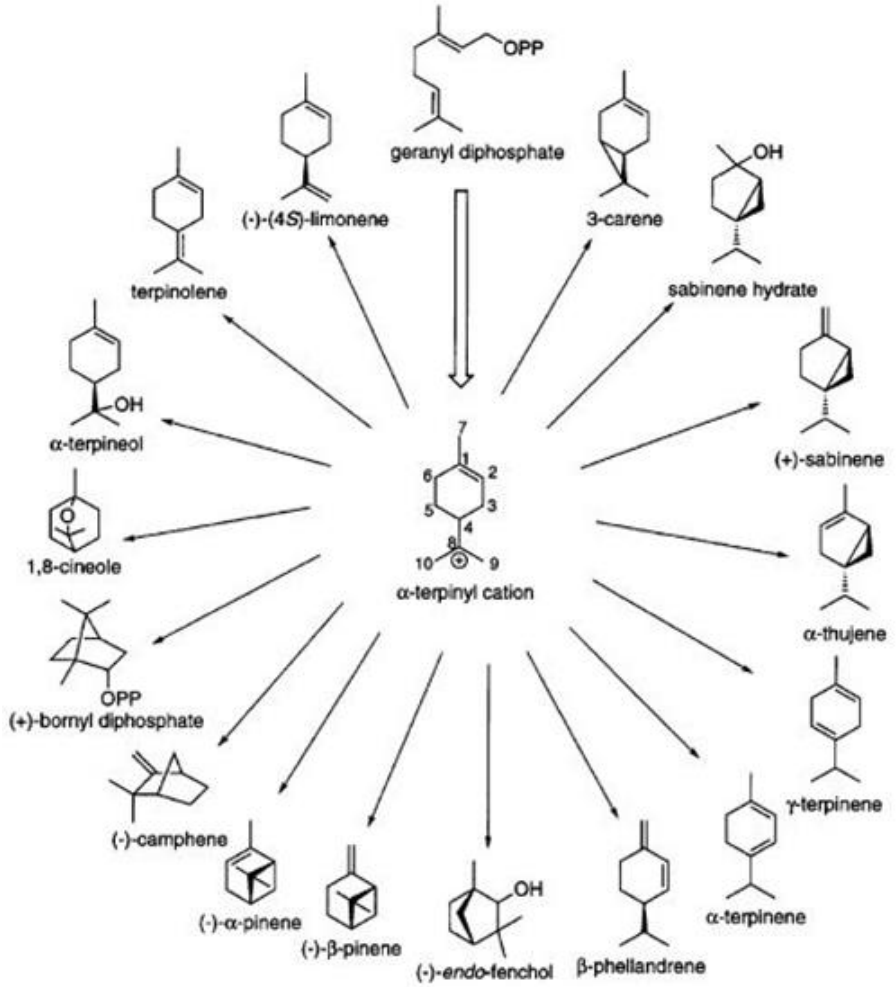


Image sources: en.wikipedia.org, examiner.com, naturesbounty.ca

Terpenes: a diverse natural toolkit



Over 74,000 known small molecule terpenes are known

Cyclization of simple precursors generates enormous diversity

Functions range from hormones to structural components

- Antimicrobials are among the most common

Christianson, D. W. *Chem. Rev.* 2006, *106*, 3412.

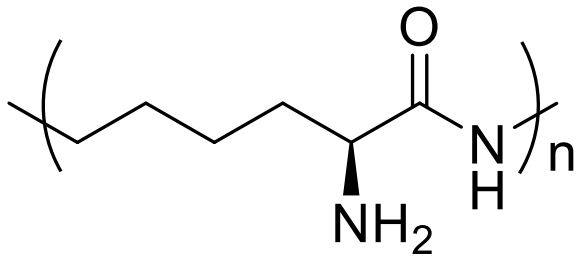
Precedent for use in home and personal care products

Common in perfumes, aromatherapy, cleaning products

Added as pure compounds or essential oils

Image sources: shop.seventhgeneration.com, www.beautycounter.com

Antimicrobial peptides are safe food preservatives



Polylysine

Chemically or biosynthetically prepared

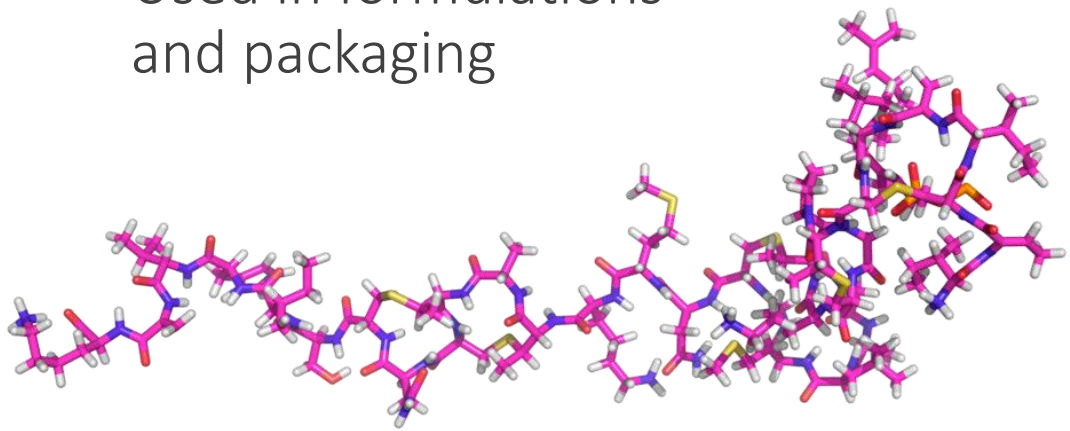
- Usually expensive

Sensitive to enzyme hydrolysis

Limited use against Gram-positive bacteria

Two examples used in food

- Inexpensive
- FDA approved GRAS (Generally Recognized as Safe)
- Used in formulations and packaging



Nisin

Image source: en.wikipedia.org

Flavonoids have diverse functions in plants

Secondary plant metabolites

Found in fruits, vegetables, nuts, seeds, flowers, and plant-based products

Functions:

- Pigments in flowers
- UV-B radiation protection agents in leaves
- Antimicrobials against fungal pathogens


Pigment


Tea


Coffee


Parsley


Herbs


Honey

Image sources: www.webexhibits.org, www.organicfacts.net, bayfieldcoffeecompany.com, www.swansonvitamins.com, www.henrietttes-herb.com, en.wikipedia.org

Precedents for use

Common in household and cosmetics products

- By-products in plants extracts and essential oils

Possible pharmaceutical use

- Synthetic modifications for new antimicrobials in medicine

Image sources: www.dermstore.com, www.q2bi.com, www.beautycounter.com

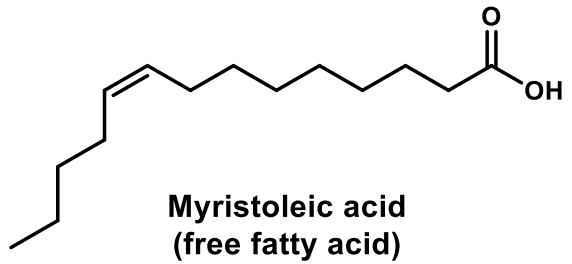
Antimicrobial lipids are multifunctional ingredients

Advantages

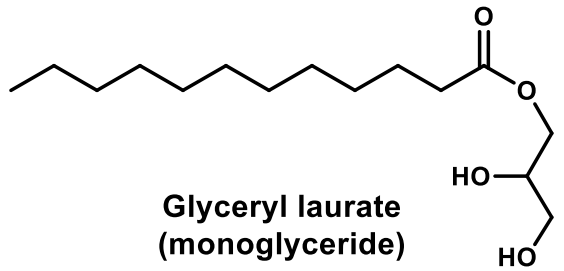
- Naturally derived from vegetable oils
- Inexpensive
- Naturally abundant on human skin
- Common ingredients in cosmetics
  - Emollient, emulsifier, surfactant

Disadvantages

- Limited activity against Gram-negative bacteria



Myristoleic acid
(free fatty acid)



Glyceryl laurate
(monoglyceride)

Image source: www.beautymakeup.gr

Proposed alternatives have comparable efficacy to conventional preservatives

	Terpenes	Peptides	Flavonoids	Fatty Acids	Parabens
Yeast	++	++	+++	+++	++
Mold	++	++	++	++	++
Gram-positive Bacteria	+++	+	++	+++	+
Gram-negative Bacteria	+++	+++	+++	+	+

\+ low efficacy
++ moderate efficacy
+++ high efficacy

Hazards might be avoided at low concentrations

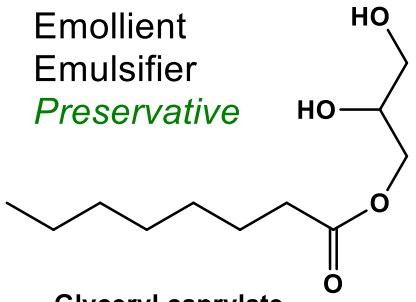
	Terpenes	Peptides	Flavonoids	Fatty Acids	Parabens
Skin Irritation	2	DG	2	3	3
Skin Sensitization	2	DG	1	DG	3
Respiratory Sensitization	2	1	2	1	2
Endocrine Activity	1	DG	3	DG	3
Biodegradability	1	1	1	1	1

1: low hazard 2: medium hazard 3: high hazard DG: data gap

Take advantage of multifunctional ingredients

1. Monoglycerides

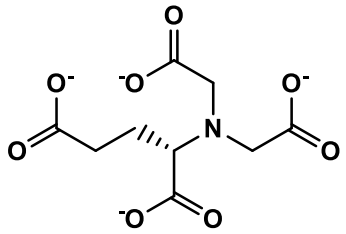
Surfactant
Emollient
Emulsifier
Preservative



Glyceryl caprylate

2. Chelators

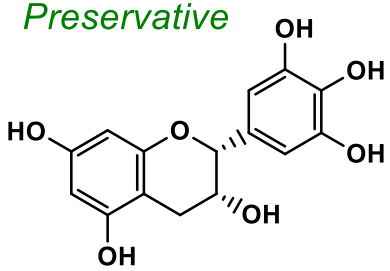
Water softener
Preservative booster



GLDA

3. Plant extracts

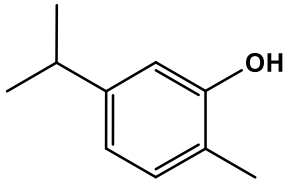
Antioxidant
Preservative



Epigallocatechin

4. Terpenes

Fragrance
Preservative



Carvacrol

Common ingredients can be exploited for their diverse properties

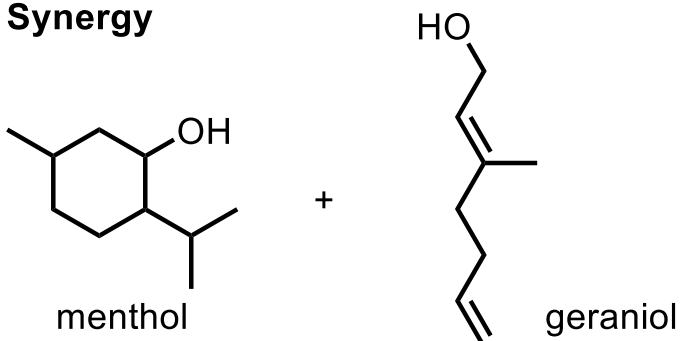
Advantages:

- **Cost**
- **Ease of formulation**
- **Consumer acceptance**
- **Regulatory compliance**

Mixtures can operate synergistically or antagonistically

1. Fractional inhibitory concentration (FIC) = (A/MIC A) + (B/MIC B)

2. Synergy



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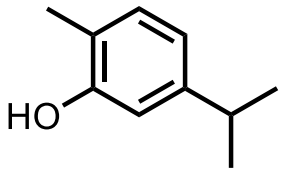
FIC (*B. cereus*): 0.06

3. Antagonism



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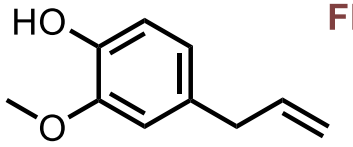


FIC (*B. cereus*): 4

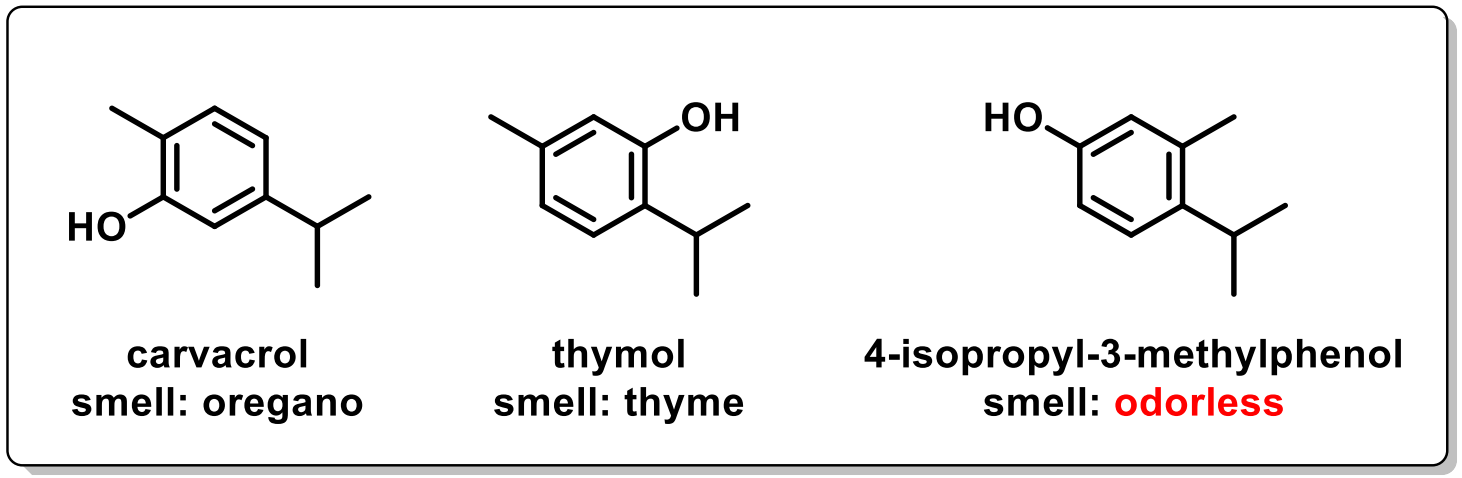
Antimicrobials may act **synergistically**, **additively** or **antagonistically**

Improve understanding for more efficient formulation

What is the optimal way to target a microbe's biochemistry?

Flavour Fragr. J. 2009, *24, 348.*

Functionally similar isomers avoid undesired qualities

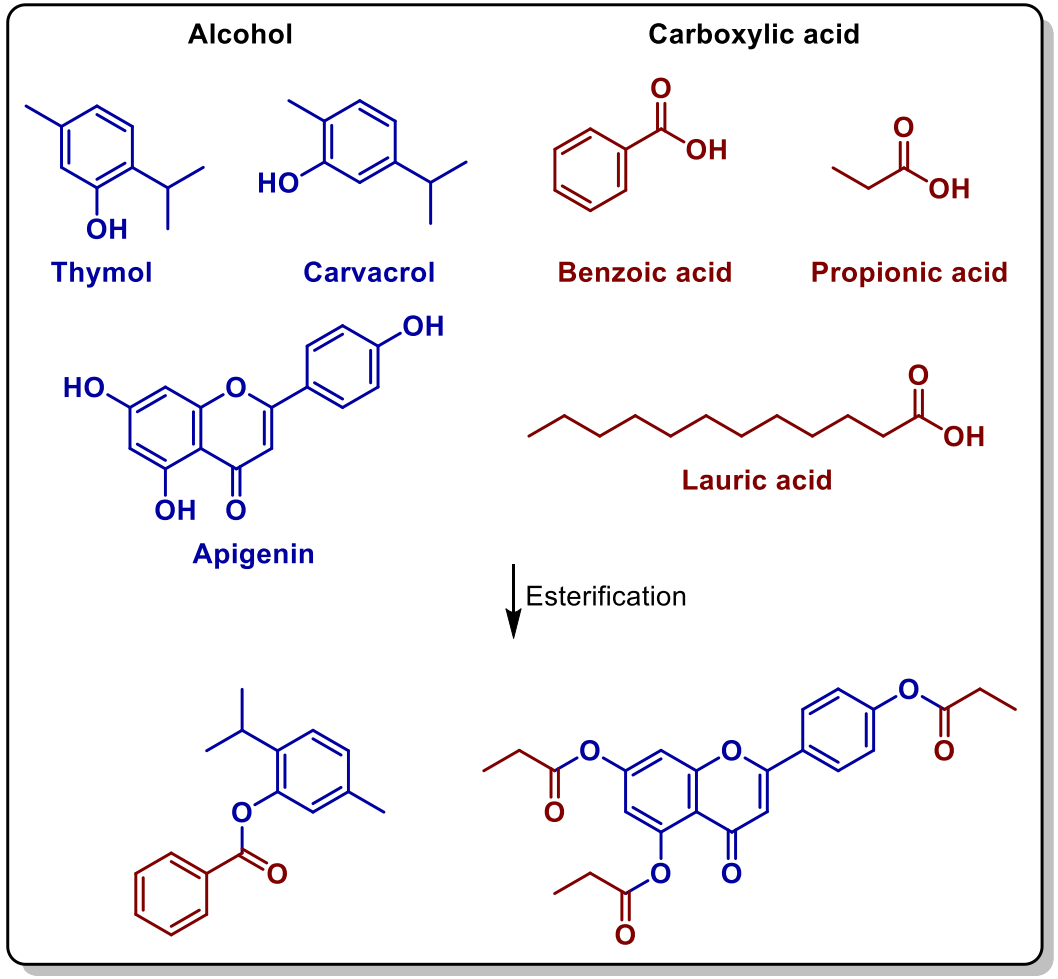


Effective antimicrobials may have potentially undesirable properties (e.g. scent)

Isomers may avoid these undesirable attributes

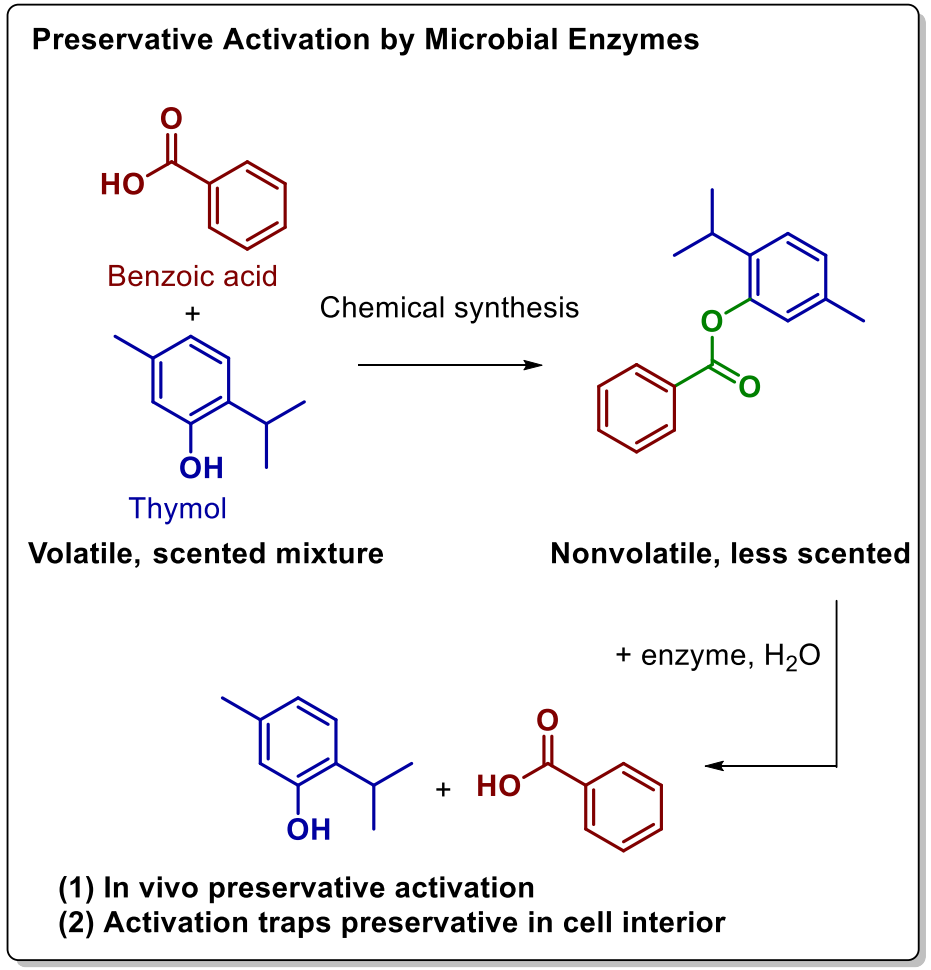
Flavour Fragr. J. 2009, *24*, 348.

Derivatization obviates unfavorable characteristics



Acta Pol. Pharm. **67,** 375–380 (2010); Image source: en.wikipedia.org

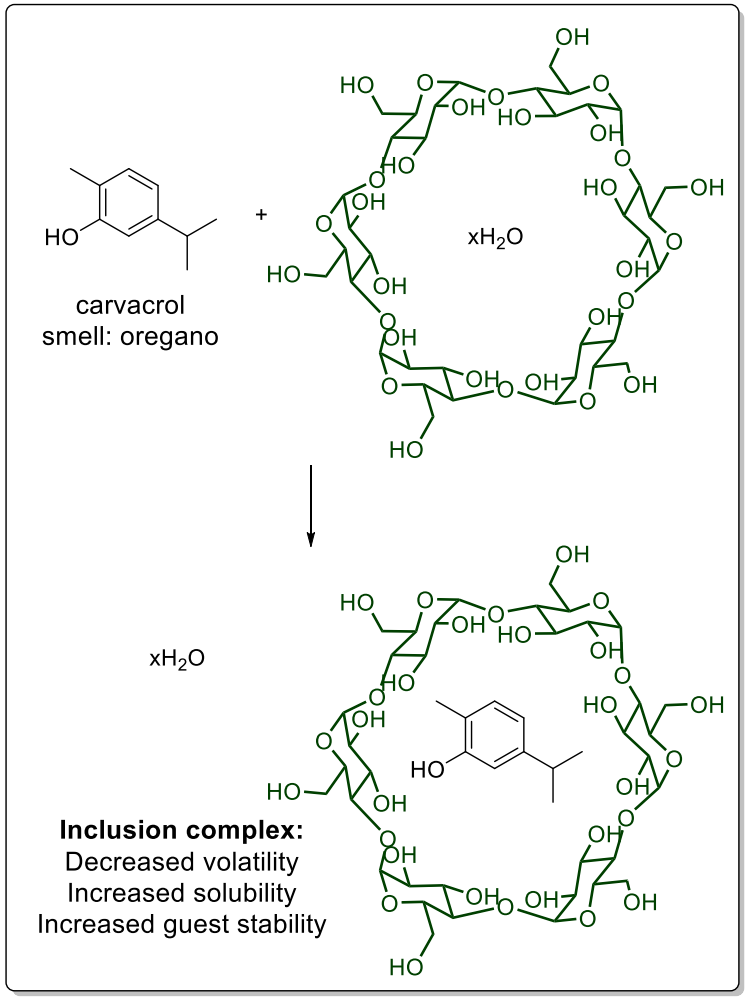
Microbial activation of a chimeric antimicrobial



In vivo **enzymatic ester cleavage** has been shown to deliver and trap molecules in the interior of cells

Antimicrobial derivatives may likewise be **activated *in vivo* by microbial enzymes**

Host-guest encapsulation improves volatility, solubility



Noncovalent inclusion of an antimicrobial in a host molecule or polymer may:

(1) **Decrease volatility, scent**

(2) **Increase solubility**

(3) **Increase guest stability**

Biosci. Biotechnol. Biochem. **64,** 731–734 (2000).

Concluding thoughts and recommendations

As drop-in replacements, terpenes, polypeptides, flavonoids, and fatty acids may be safer, effective, and biodegradable preservatives

- Subject to **data limitations**, **consumer perception**, and **regulation**

A longer view should include new chemical and non-chemical approaches

- Synergy, encapsulation, microbial hydrolysis, chimera complexes
- Innovative packaging

Industry-academia collaborations leverage expertise of both sectors

Industry players have an opportunity to **work together to protect people, products, and our planet**

Acknowledgements

Meg Schwarzman and Marty Mulvihill (Berkeley Center for Green Chemistry)

Tina Hoang, Patrick Gorman and Jeremy Faludi (Greener Solutions Class)

Mia Davis (Beautycounter) and Lauren Armstrong (Northwest Cosmetics Labs)

Chantal Bergeron, Clement Choy and Martin Wolf (Seventh Generation)

Mark Dorfman (Biomimicry 3.8)

Larry Weiss (AoBiome)

Kaj Johnson and Ryan Williams (Method)

Questions?

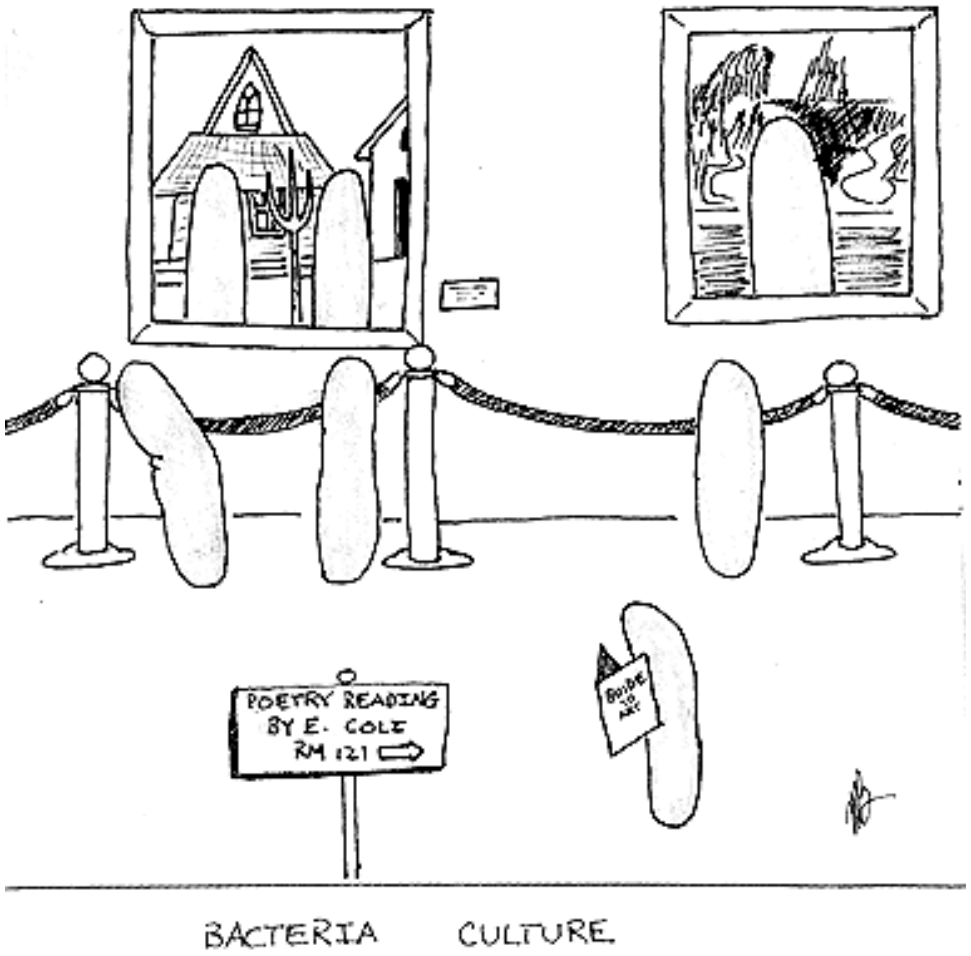


Image source: www.oocities.org