

Assuring the safety of botanicals

History of Safe Use

Paul Russell



Unilever

2.5bn
consumers
reached

48k
suppliers

190
countries

60%

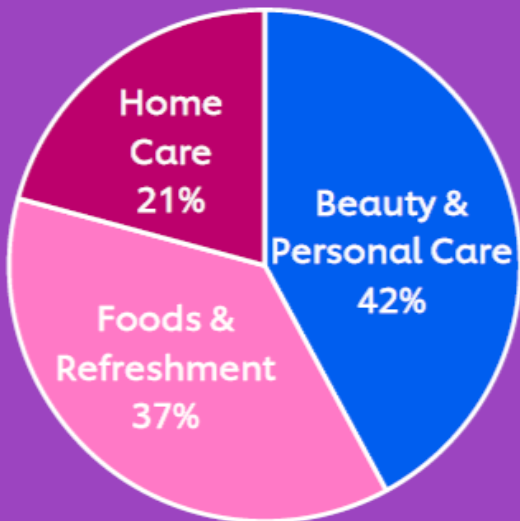
sales in emerging
markets

12
billion euro
brands

1.3bn
people helped to
improve health
and hygiene



14 of the top 50 global
consumer brands



90%
local leaders



Safety & Environmental Assurance Centre (SEAC)

PROTECTING CONSUMERS, WORKERS & OUR ENVIRONMENT BY ENSURING UNILEVER'S PRODUCTS & PROCESSES ARE SAFE & SUSTAINABLE BY DESIGN

CENTRE OF EXCELLENCE – SAFETY & ENVIRONMENTAL SUSTAINABILITY SCIENCES

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GOVERNANCE

We provide scientific evidence to manage safety risks & environmental impacts for new technologies

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NEW CAPABILITY

We harness the latest science to create new tools to assess innovations of the future

SHARING SCIENCE



COLLABORATION

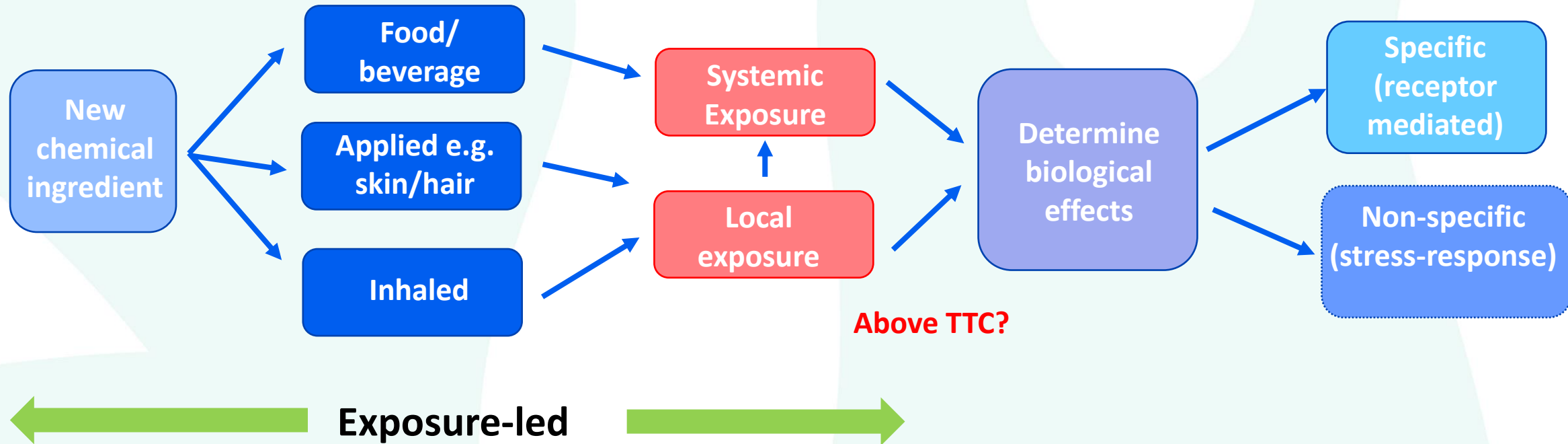
We partner with leading scientists from around the globe

Can we use a new ingredient safely?

- Can we safely use **x%** of ingredient **y** in product **z**?



Exposure-led risk assessments



Do you have a favourite?

'Everything is poison, there is poison in everything. Only the dose makes a thing not a poison.' Paracelsus



Amygdalin
(0.6g/kg seeds)



1.1 kg apple
seeds



Formaldehyde
(0.06g/kg)



116 kg
pears



Solanine
(0.2g/kg)



79 kg
potatoes



Cucurbitacin E
(0.25-7 g/kg,
high in bitter courgettes)



119 kg
courgettes

Naturals in cosmetics

- There is now a growing consumer demand for cosmetic products which contain botanical derived ingredients with established or perceived functional benefit.
- Sales volumes have therefore increased for natural or organic cosmetics.
- Public believe that natural ingredients are safer than synthetic ingredients.



'History of Safe Use' Risk Assessment

- Risk assessment of botanical materials (herbals, traditional Chinese medicines, Ayurvedics etc) which have a long history of use in certain parts of world.
- 'History of Safe Use' (HoSU) is widely used for safety assessment of food ingredients (e.g. novel foods and foods derived from genetically modified organisms) and the principles can be extended for cosmetic products.
- History of safe use assessments need to be robust, transparent and evidence based.
 - Identification of suitable comparator with a history of prior use
 - Evidence for toxicological concern (and lack of concern) of the comparator.
 - The similarity of the botanical of interest with the comparator.

Useful references:

History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms; Constable, A et al, Food and Chemical Toxicology; 45 (12) (2007); 2513-2525.

A multi-criteria decision analysis model to assess the safety of botanicals utilizing data on history of use; Neely, T et al; Toxicology International; 18 (2011); 20-29.

Evidence of History of Use (Exposure)

- Origin of ingredient
- Similarity of ingredient specification
- Preparation and processing similarity
- Similarity of population to be exposed especially products aimed at babies/children - comparator should have similar history of exposure
- Number of people exposed
- Pattern of use/frequency of application
- Bioavailability/Skin penetration

Naturally challenging

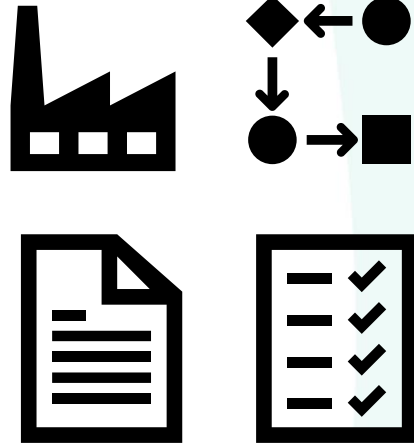
Raw Material Identification

e.g. Which Ginseng?
American, Korean,
Chinese, Indian...



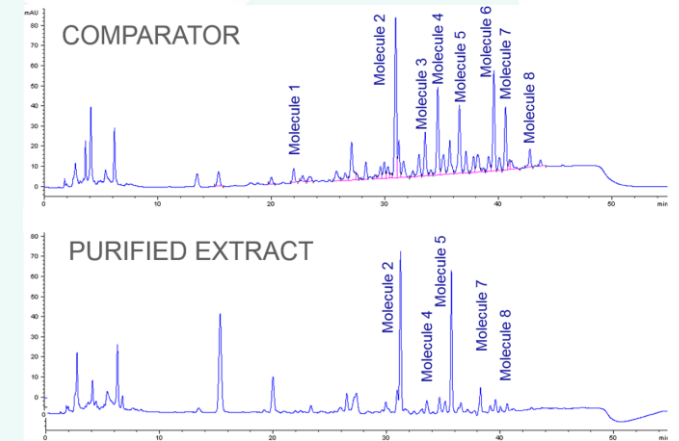
Specification control

- Processing
- Marker compounds
- Mass balance?



Chemical analysis

- Fingerprinting
- Targeted quantitation



Control of sample variation: Natural plant variation, geographical, seasonal, age...

Start with the basics

Authenticate the raw material

Slimming Aids

- *Aristolochia* spp
- Renal failure in ~300 patients worldwide
- aristolochic acid containing fangchi species substituted for manshuriensis



Start with the basics

Control the variation

Inter-plant



Geographical



Wounding



Seasonal



Life stage



Process



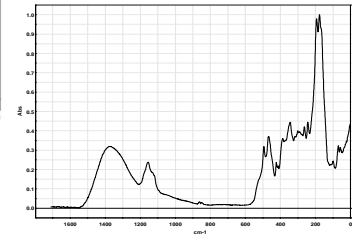
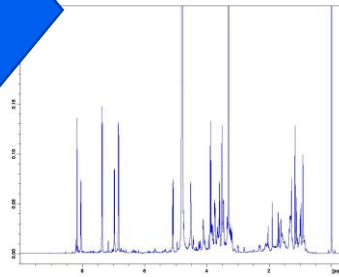
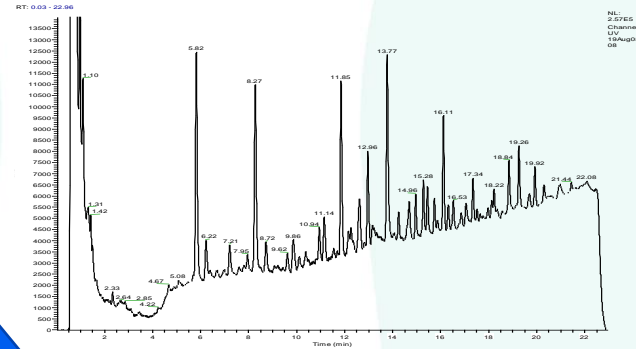
Know your material - Chemical analysis

Basic Specifications



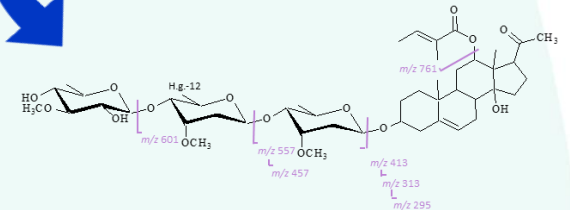
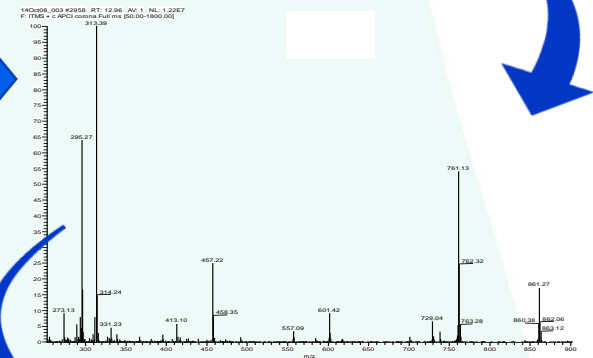
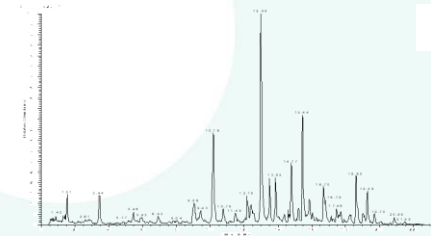
Key marker chemicals

Global Fingerprinting



HPLC-MS, NMR, FTIR

Component ID & Quantitation



Statistical techniques

1. Unsupervised Exploratory Techniques

- Principal Components Analysis
- Hierarchical Cluster Analysis

2. Similarity Analysis

- Correlation coefficient
- Congruence coefficient
- Euclidean distance
- Mahalanobis distance

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Review
Similarity analyses of chromatographic herbal fingerprints: A review
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HIGHLIGHTS

- Similarity analyses of herbal fingerprints are reviewed.
- Different (dis)similarity approaches are discussed.
- (Dis)similarity-metrics and exploratory-analysis approaches are illustrated.
- Correlation and distance-based measures are overviewed.

GRAPHICAL ABSTRACT

Two chromatograms are shown, separated by an equals sign. The right chromatogram has a large question mark next to it.

ABSTRACT

...ing again more popular in the developed countries because being "natural" are inherently safe. Herbs have also been used worldwide for many years. The concern of their safety and efficacy has grown since increased use. The chemical constituents are very complex, often including hundreds of compounds. The chemical constituents are very complex, often including hundreds of compounds. The chemical constituents are very complex, often including hundreds of compounds.

Evidence for Concern (Hazard)

Toxicology data

- High Concern: Reproductive or developmental toxicity, mutagenicity, neurotoxicity or any organ toxicity, data showing skin sensitization (type IV allergy), type I allergy, skin carcinogenicity, phototoxicity effects

Chemical components of concern

- High concern: known skin sensitisers, photoallergens, proteins....
- Biological effects/mechanism of action
- Evidence of adverse effects in man (Information from literature review or existing clinical data)

Useful Data Sources

- Food Standards Agency: <https://www.food.gov.uk/>
- European Food Safety Authority (EFSA) - <http://www.efsa.europa.eu/> ,
<https://www.efsa.europa.eu/en/topics/topic/dietary-reference-values>
- World Health Organization - https://www.who.int/foodsafety/areas_work/nutrition/en/
- Health Canada - http://recherche-search.gc.ca/rGs/s_r?st=s&langs=eng&st1rt=0&num=10&cdn=health
- JECFA - Monographs & Evaluations - <https://www.who.int/foodsafety/publications/monographs/en/>
- U.S. Food and Drug Administration - <https://www.fda.gov/food>
- Natural Medicines Comprehensive Database - www.NaturalMedicines.com/login
- European Medicines Agency - <https://www.ema.europa.eu/en/committees/committee-herbal-medicinal-products-hmpc>
- PubMed - <https://www.ncbi.nlm.nih.gov/pubmed?tool=csl&otool=cslotool>
- Toxicology Data Network (TOXNET) - <https://toxnet.nlm.nih.gov/>
- Personal Care Products Council - <http://online.personalcarecouncil.org/jsp/Home.jsp>
- Chemical Safety Information from Intergovernmental Organizations - <http://www.inchem.org/>

Case Study: Green tea in skin cream



Green tea in skin cream

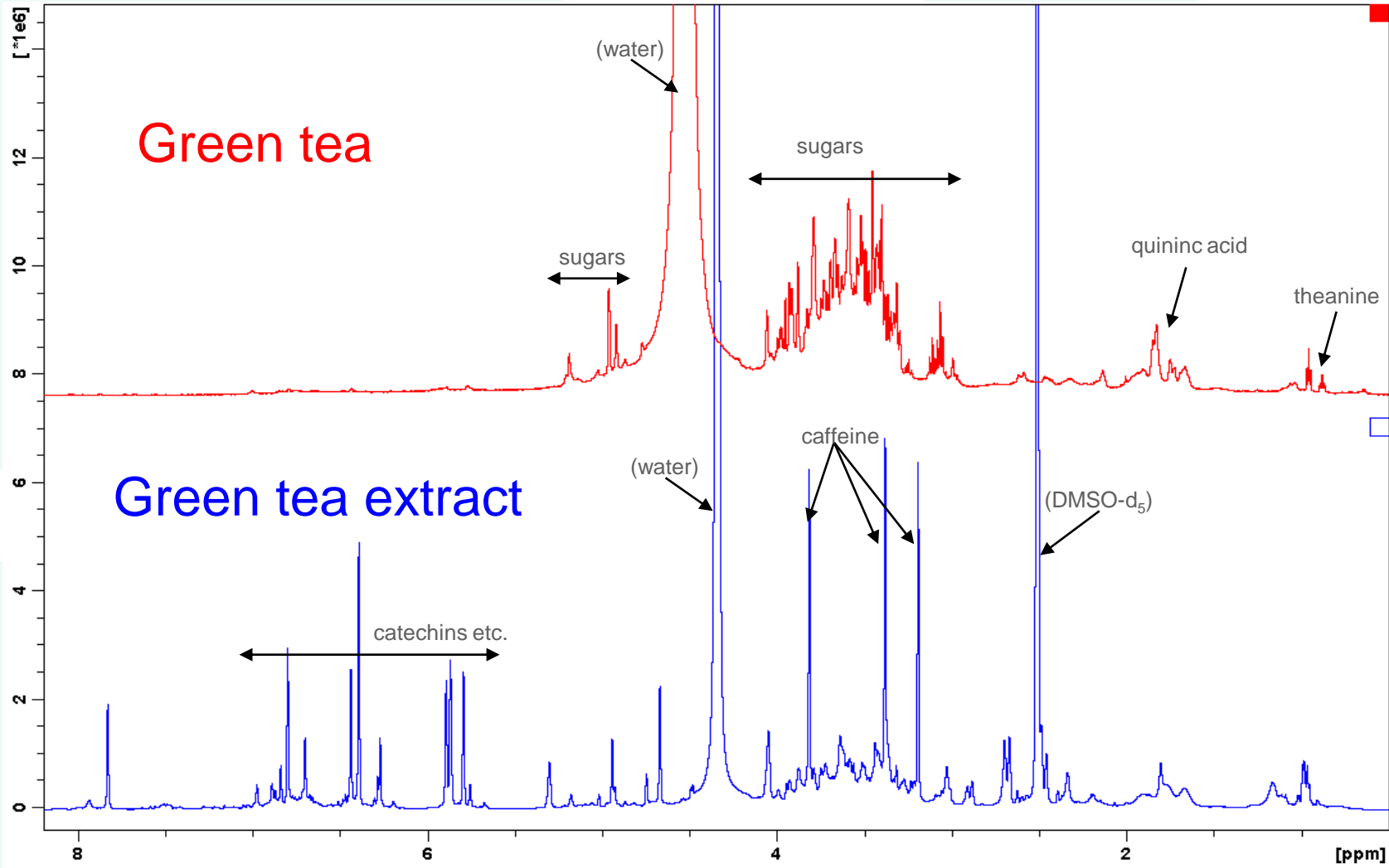
- Green tea (*Camelia sinensis*)
- Traditionally drunk as a hot beverage – some history of topical use
- Large amount of historical oral consumption information
- The primary chemical components are polyphenols
- Safety assessment was needed for inclusion of green tea extract in a leave-on skin product
- History of Safe Use approach used



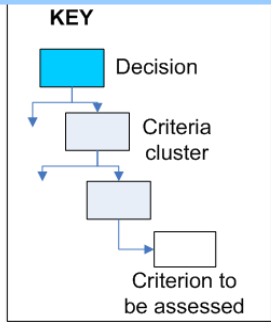
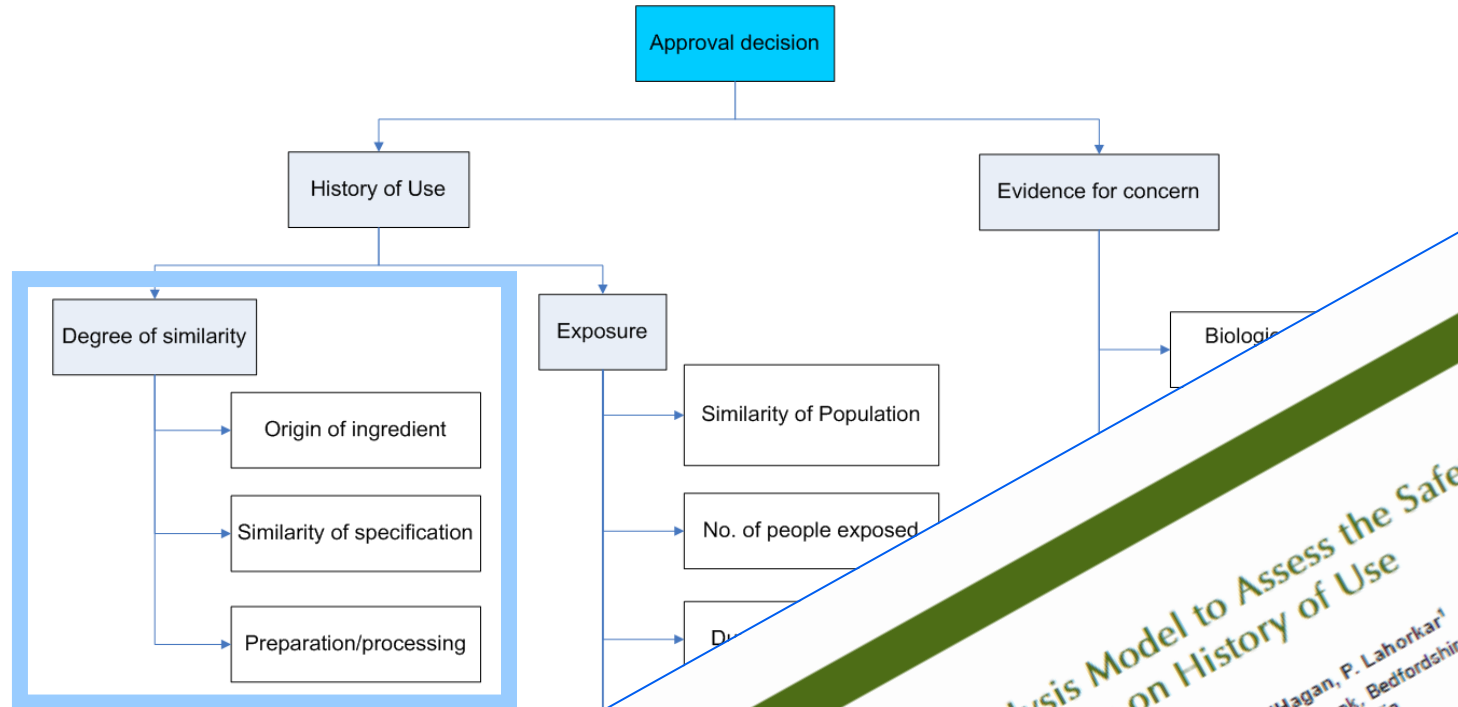
Information Gathering

Criteria	Response for green tea	Evidence
Origin of ingredient	Identical to traditional/comparator	<i>Camelia sinensis</i> leaves used. Harvested in SA Asia for tea production
Similarity of specification	Almost the same	Fingerprint and quantitative assessment of components confirms similar specification
Preparation and processing	Almost the same	Aqueous extract – prepared by boiling dried leaves
Populations	Use encompasses population intended to expose e.g. healthy adult females	Evidence of topical use of green and black tea
No. of people exposed	Thousands	Evidence of topical use reported in open literature
Duration of exposure	20 years +	Evidence of topical use reported in open literature
Pattern/frequency of use	Ingested and topically applied on a daily basis	Evidence from Natural Medicines Database
Bioavailability	Not known	-
Toxicological data	Some data showing green tea extracts to cause skin sensitisation when applied topically	Literature search (numerous references)
Chemical components of concern	Catechins	Literature search (numerous references)
Biological effects/mechanism of action	Catechins may have anti-inflammatory activity	Evidence from Natural Medicines Database
Evidence of adverse effects in man	Some evidence of irritation when used at high concentrations in topical applications	Literature search (numerous references)

Green Tea - Composition analysis



History of Safe Use (HoSU)



Research Article

A Multi-Criteria Decision Analysis Model to Assess the Safety of Botanicals Utilizing Data on History of Use

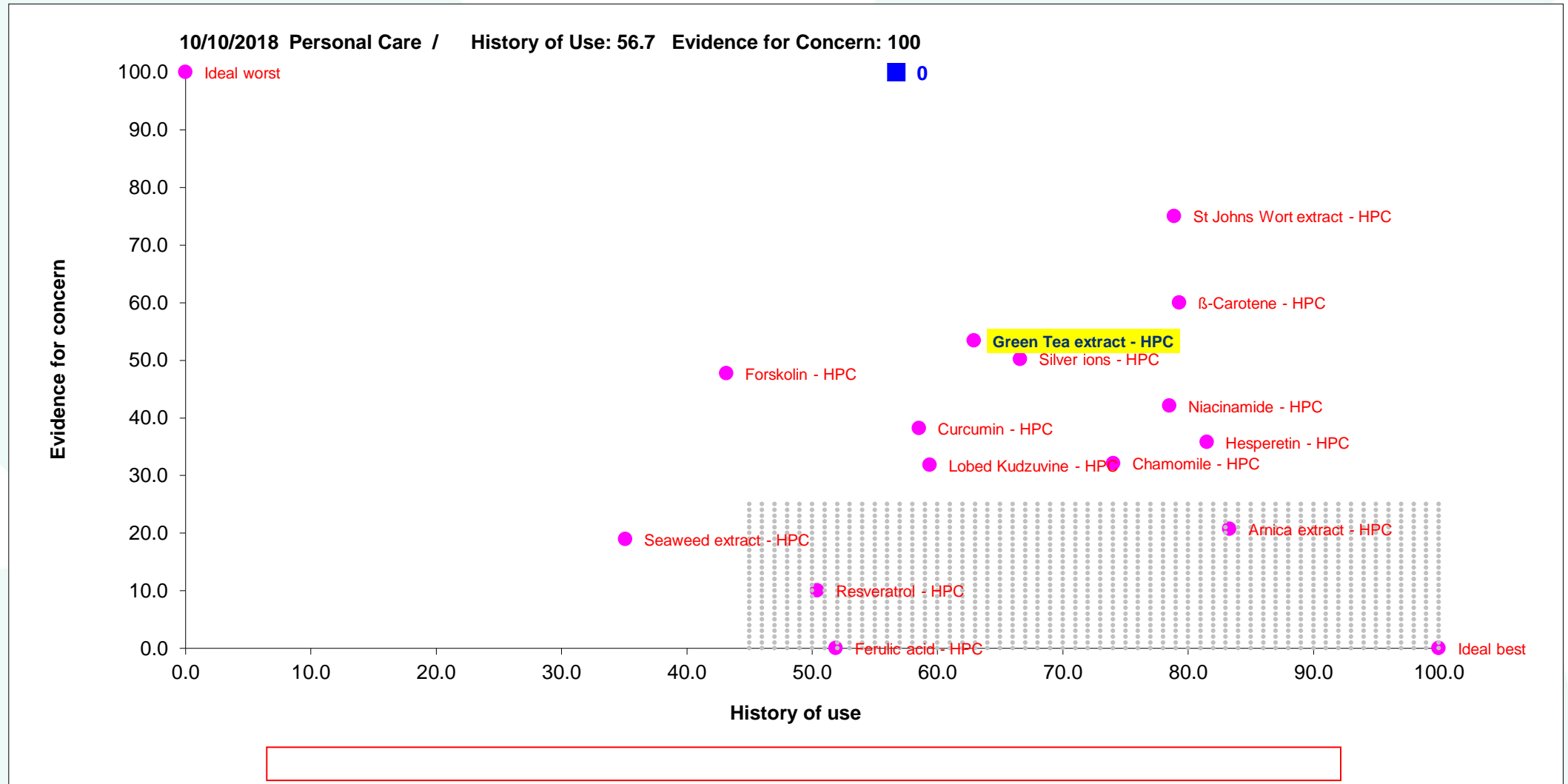
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ABSTRACT

Botanicals and extracts are widely used in traditional medicines throughout the world. Many have been used for safe use over several hundreds of years. There is now a growing consumer interest in food products that contain botanicals. There are many publications describing the safety assessment of botanicals, but the history of safe use. However, they do not define what constitutes a history of safe use. The multi-criteria decision analysis (MCDA), is a model for the safety of botanical ingredients using a history of use approach. The objective of interest to its historic counterpart – the comparator, the history of use. In order to establish compositional similarity (Bacopa monnieri), the assessment made is whether a botanical ingredient is similar to its historic counterpart – the comparator. The MCDA approach is transparent, and transferable safety assessment.



Benchmarking the output – Unilever HoSU model



Risk assessment outcome

- Not supported for the desired use scenario based on high evidence of concern
 - High catechin levels associated with skin sensitisation
- Further hazard and exposure data would be required to refine the assessment
 - In vitro assays to assess sensitisation hazard
 - Skin penetration measurement/prediction



Summary

- Exposure led risk assessment is essential to confidently assess the safety of an ingredient for specific use scenarios
- History of safe use assessments use available data to inform decision making or identify next steps for refinement
- Analytical chemistry is key for characterising the exposure for novel extracts

For more information on Unilever's ongoing research to develop non-animal approaches to safety assessment visit www.tt21c.org



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