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# Food drugs as drivers of therapeutic knowledge and the role of chemosensory qualities

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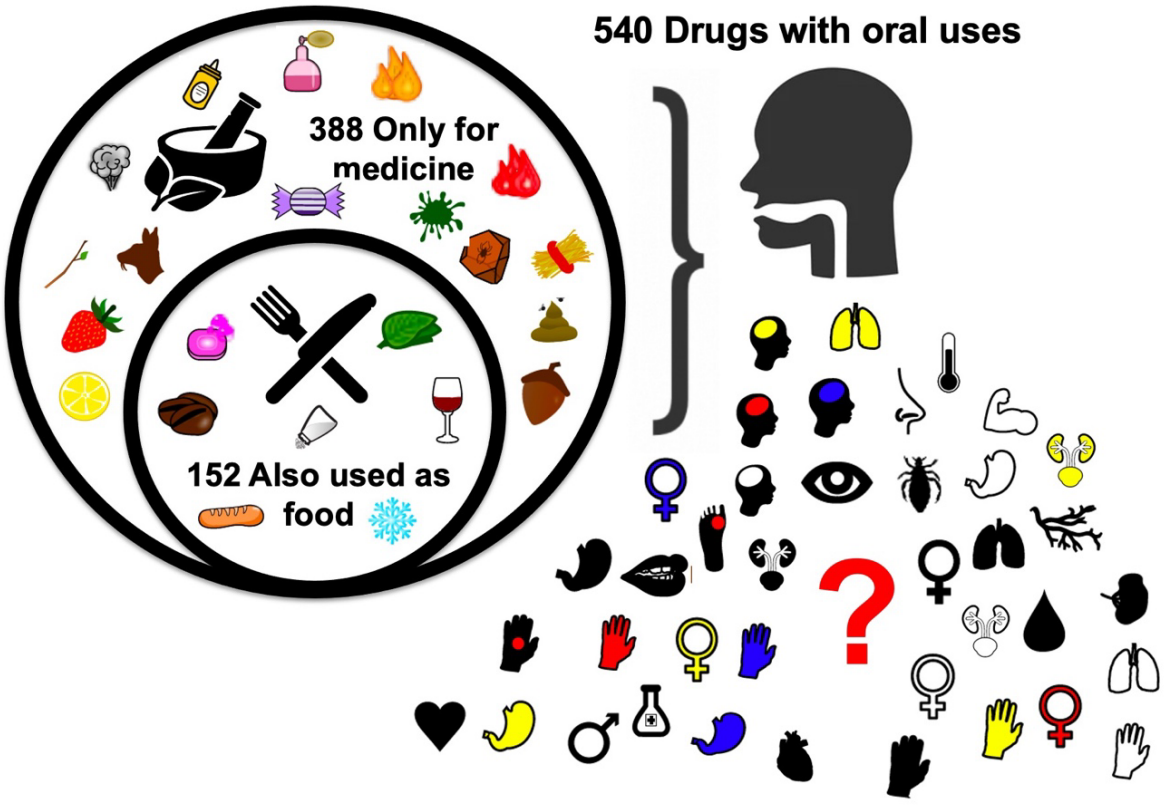

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**Abstract**

Ethnopharmacological relevance: Chemosensory qualities of botanical drugs are important cues for anticipating physiologic consequences. Whether a botanical drug is used for both, food, and medicine, or only as medicine depends on taste preferences, nutritional content, cultural background, and the individual and overall epidemiological context.

*Material and methods:* We subjected 540 botanical drugs described in *De Materia Medica* having at least one oral medical application to a tasting panel. The 540 drugs were grouped into those only used for medicine (388) and those also used for food (152). The associations with chemosensory qualities and therapeutic indications were compared across the two groups. We considered 22 experimentally assessed chemosensory qualities and 39 therapeutic use groups. We wanted to know, 1): which chemosensory qualities increase the probability of an orally applied botanical drug to be also used for food ?; 2): which chemosensory qualities augment the probability of an orally applied botanical drug to be only used for medicine?; and 3): whether there are differences in therapeutic indications between orally applied botanical drugs also used for food (food drugs) and botanical drugs applied exclusively for medicinal purposes (non-food drugs) and, if yes, how the differences can be explained.

*Results:* Chemosensory qualities augmenting the probability of an orally applied botanical drug to be also used for food were sweet, starchy, salty, burning/hot, fruity, nutty, and cooling. Therapeutics used for diarrhoea, as libido modulators, purgatives, laxatives, for expelling parasites, breast and lactation and increasing diuresis, were preferentially sourced from food drugs while drugs used for liver and jaundice, vaginal discharge and humoral management showed significant negative associations with food dugs in ancient Greek-Roman *materia medica*.

*Conclusion*: Therapeutics used for ailments of body organs involved in the digestion of food and the excretion of waste products showed a tendency to be sourced from food drugs. Arguably, the daily consumption of food offered the possibility for observing post-prandial physiologic and pharmacologic effects which led to a high therapeutic versatility of food drugs and the possibility to understand benefits of taste and flavour qualities. The difference

in chemosensory qualities between food drugs and non-food drugs is demarcating the organoleptic requirements of food rather than that of medicine.

**Keywords:** Taste receptor pharmacology, food drugs, historical studies, *De Materia Medica*, co-evolution food-medicine, ethnopharmacology, ethnobiology

## 1. Introduction

Food distinguishes from medicine in that it is generally consumed daily, with a focus on palatable nourishment while medicines are often prescribed and taken for limited periods and specific therapeutic purposes. Food intake is guided by olfaction, gustation and chemesthesis (Goff and Klee, 2006; Yarmolinsky et al., 2009; Breslin, 2013; Palmer and Servant, 2022). The perception of taste and flavour (a combination of taste, smell and chemesthesis) have evolved matching nutritional requirements and are particularly important in omnivores for detecting palatable and rejecting toxic and deteriorated food (Rozin and Todd, 2016). However, humans have learned to use unpalatable and toxic substances for medicine (Mann, 1984; Johns, 1990; Mennella et al., 2013). It is thought that plant-based medicine is rooted in diet and the search for nutrition and that agricultural practices refined and diversified associated knowledge (Johns, 1990; 1999; Etkin, 1994; Logan and Dixon, 1994, Brown, 1985; Leonti et al., 2006). In theory all food may be regarded therapeutic by someone who's hungry (Etkin and Ross, 1991) but whether a food item is perceived only as food or also as a therapeutic or prophylactic agent depends more specifically on culture and epidemiology (Etkin and Ross, 1982; 1991; Johns, 1990; Etkin, 2008; Lindeberg, 2010).

The origin of the frequent saying "let food be thy medicine and medicine be thy food", is unclear and not to be found in the *Corpus Hippocraticum* (Cardenas, 2013; Totelin, 2015). The misquotation of the *Corpus Hippocraticum* ($6^{th}$ to $2^{nd}$ century BCE) in this context is probably due to the many substances described in Classical Greece that were explicitly used as food medicines (Wilkins, 2015, Totelin, 2015; 2018a). Also today, from the 219 herbal drugs listed in the European Pharmacopoeia 9.5, (2017), 75 (≥ 33%) are used for both, food as well as medicine (European Pharmacopoeia 9.5, 2017; **Supplementary Table A**). Similar values can be expected for European herbal medicine in general and probably higher ones for the Ayurvedic and Chinese pharmacopoeias (c.f.e.g., Wichtl, 2002; The Ayurvedic Pharmacopoeia of India (API), 2001-2016; Chinese Pharmacopoeia (ChP), 1997).

In Classical antiquity, the power of botanical drugs was extrapolated from their taste (Jones, 1959; Einarson and Link, 1990; Jouanna, 2012; Totelin, 2018b). According to the Greek physician Mnesitheus of Athens (4th century BCE) “all salt and sweet juices move the bowels. But acid and pungent foods stimulate urine; bitter juices are more diuretic, and some loosen bowels and astringent ones check excretion” (Baker, 2018). Theophrastus (300 BCE) reports that sweet has the capacity to smoothen, astringent the power to desiccate and solidify, pungent the capacity to cut or to separate out heat, salty the power to desiccate and irritate, and bitter the capacity to melt and irritate (Einarson and Link, 1990). Today, in Western herbal medicine, the use of chemosensory qualities is limited to quality and identity control of botanical drugs (e.g., Wichtl, 2002; Gafner et al., 2023) but are still important cues for the prescription of medicines in Ayurvedic and Traditional Chinese Medicine (Patwardhan et al., 2004; Maciocia, 2015).

In a study using tasting-panel data applying a phylogenetic approach, we have recently shown how in ancient Graeco-Roman society the use of botanical drugs was shaped by chemosensory qualities (Leonti et al., 2024). However, a study focusing on the differences of experimentally assessed chemosensory qualities and recorded therapeutic uses of food drugs and non-food drugs has never been made so far. We expect such an exploratory analysis to provide insights into the dietary or non-dietary origin of specific therapeutic knowledge possibly linked to specific chemosensory qualities. Here, we therefore compare chemosensory qualities and ancient therapeutic uses of orally applied botanical drugs that are commonly used in diet (food drugs) and chemosensory qualities and uses of botanical drugs generally only used for therapeutic purposes (non-food drugs) as recorded in Dioscorides’ *De Materia Medica* (*DMM*). We address the following questions: 1): Which chemosensory qualities augment the probability of an orally applied botanical drug to be also used for food?; 2): which chemosensory qualities augment the probability of an orally applied botanical drug to be only used for medicine?; and 3): Are there significant differences in the frequency of therapeutic indications between orally applied food drugs and orally applied botanical drugs used exclusively for medicinal purposes, and, if yes, how can these differences be explained?

## 2. Methods

### 2.1. Sampling of the data set

We collected 700 botanical drugs recommended in *De Materia Medica* (*DMM*; ex Matthioli, 1967–1970) corresponding to around 70% of all botanical drugs described in *DMM*. The

associated use records were arranged into groups of therapeutic use, according to affected organs, therapeutic functions, diseases, and symptoms described in *DMM*, permitting for statistical analysis. More details on species selection, identification and plant drug collection are presented in Leonti et al. (2024). From the 700 drugs in our database, we selected all those recommended for oral applications resulting in a dataset including 540 botanical drugs arranged into 39 therapeutic use groups (**Table 3; Supplementary Tables 1 and 2**). We then divided the 540 drugs between those that have reported dietary uses (food drugs) across history (vegetables, fruits, spices, condiments, and drugs used for the preparation of liquors; **Supplementary Table 2**) and those that are generally not used in diet (non-food drugs: herbal drugs used for infusions, decoctions, tinctures, but also for the preparation of liquors; **Supplementary Table 1**). The separating line was set between spices such as cinnamon (bark of *Cinnamon* sp.) fruits of fennel (*Foeniculum vulgare*) and anis (*Pimpinella anisum*) that were assigned to the food drugs and drugs used for the preparation of infusions and liquors such as the herb of lemon balm (*Melissa officinalis*), the inflorescences of chamomile (*Matricaria chamomilla*) or the root of gentian (*Gentiana lutea*, Gentianaceae), that were assigned to the non-food drugs. Rue (*Ruta* sp.) also used as a condiment in Roman times (Apicius, 1991) was classified as medicine. Herbal drugs mentioned in *DMM* exclusively for being edible and without any therapeutic indications were not considered in this analysis[1]. This resulted in a group of 388 non-food drugs associated with 1407 use records and a group of 152 food drugs, associated with 648 use records (**Supplementary Tables 1 and 2**). Latin binomials follow https://powo.science.kew.org/.

### 2.2. Tasting panel

A tasting panel consisting of eleven Caucasian panellists tasted the 540 botanical drugs for the perception of 22 chemosensory qualities. A total of 2210 taste trials were conducted for the non-food drugs (5.7 trials on average; **Supplementary Table 3**) and 845 taste trials were conducted for the food drugs (5.6 trials on average; **Supplementary Table 4**). The tasting panel did not distinguish between salty and umami (savoury tastes) and included the

[1] The leaves of *Arum maculatum* L. (Araceeae), *Smyrnium olusatrum* L. (Apiaceeae), *Solanum nigrum* L. (Solanaceae), *Ulmus minor* Mill. (Ulmaceae), *Atriplex halimus* L. (Amaranthaceae), *Raphanus raphanistrum* L. (Brassicaceae), *Eryngium maritimum* L. (Apiaceae) and *Zingiber officinale* Roscoe (Zingiberaceae), the herbs of *Glebionis coronaria* (L.) Cass. ex Spach (Asteraceae), *Plantago coronopus* L. (Plantaginaceae), *Cynara cardunculus* L. (Asteraceae), *Silybum marianum* (L.) Gaertn. (Asteraceae), *Clematis vitalba* L. (Ranunculaceae) and *Orobanche* sp. (Orobanchaceae), the fruits of *Crataegus germanica* (L.) Kuntze (syn.: *Mespilus germanica*; Rosaceae) and *Ficus sycomorus* L. (Moraceae), the root of *Cyperus papyrus* L. (Cyperaceae), the seeds of *Persicaria hydropiper* (L.) Delarbre (Polygonaceae), the seed and root of *Nelumbo nucifera* Gaertn. (Nelumbonaceea), as well as the root and herb of *Pastinaca sativa* L. (Apiaceae) are not included in this analysis.

taste of glutamic acid salts among the perception of salty (see Ninomiya, 2015 for further discussion). The detailed experimental procedure of the tasting panel is described in Leonti et al. (2024).

### 2.3 Plant parts and plant families

Different plant organs and derivatives, such as roots, fruits, seeds, leaves, barks, flowers, and exudates have characteristic textures and profiles of primary and secondary metabolites across plant families. Since texture and chemical composition of plant tissues determine their dietary value as well as their chemosensory qualities, we also report plant parts used across both, food drugs and non-food drugs, along with the most important plant families (in terms of number of species).

### 2.4. Statistics

For the estimation of the effect of chemosensory perception on the concomitant use for food of orally applied botanical drugs we used a Bayesian logistic model with vague prior distributions on model parameters. The statistical unit consisted of botanical drugs assessed by a tasting panel whose score was set 1 (success) when the drug is also used for food and 0 (failure) if otherwise. The model includes a random effect for chemosensation, assuming that its effect on the concomitant use for food is not constant. Chemosensation was scored on a scale between 0 (absent) to 3 (strong) for each of the 22 qualities.

We tested for chemosensory qualities showing a significant positive or negative tendency on the concomitant use of botanical drugs for food and for chemosensory qualities showing a significant positive or negative tendency on an exclusively medical use, both with more than 90% probability. This type of Bayesian model is a standard approach for analysing data and has been widely used (see for instance, Gómez-Rubio, 2020). With the Bayesian model we can incorporate all chemosensory qualities and intensities into a unified evaluation. It enables us to estimate the effects of chemosensory perception on the concomitant use of botanical drugs for food, accounting for the fact that the influence of chemosensation on the use of a botanical drug may not be constant. By considering all chemosensory qualities concurrently, we can account for the complex interplay of different qualities and their influence on the use of botanical drugs for food and medicine (**Figs. 1 and 3**).

The simple boostrap approach of separate analyses of the frequency of use given a chemosensory quality, permits to show associations of specific qualities with a concomitant use for food or solely for medicine, but it cannot provide an overall assessment of the

influence of different qualities on use because each quality is analysed singularly (**Figs. 2 and 4**). It provides an illustrative representation of the original data, highlighting the mean quality values alongside the 95% bootstrap confidence intervals. Impacts on use caused by interactions of different chemosensory qualities are therefore not addressed by this analysis (**Figs. 2 and 4**). For the estimation of the associations of therapeutic uses with the two groups of orally applied botanical drugs we used a classical log-linear model over the contingency table. As a cutoff for significance, we used a value of $p < 0.005$ which corresponds to a minimum probability of a false discovery (i.e., declaring significance when there isn't) of around 6.7% (Benjamin et al., 2018). The statistical unit consisted of botanical drugs which were set 1 (success) when the drug was used for a certain therapeutic use and 0 (failure) when the specific use was absent.

## 3. Results

### 3.1. Effect of chemosensory qualities on the probability of an orally applied botanical drug to be also used for food or to be exclusively used for medicine

More intense perceptions of sweet, starchy, salty, burning/hot, fruity, nutty, and refreshing qualities were significantly associated with food drugs while intense bitter and astringent tastes were negatively associated with food (**Fig. 1**). The associations between the intensities of the significant qualities, and the frequencies of specific therapeutic uses of food drugs are reported in **Fig. 2**. Warming, aromatic and pungent qualities showed positive associative tendencies with food drugs without being significant, while negative tendencies were observed for woody, stinky and smoky tastes (**Supplementary Fig. 1**). The situation for the non-food drugs was inverse (**Figs. 3 and 4, Supplementary Fig. 2**). The individual relative perception of specific chemosensory qualities across all 540 drugs showed a high variation among panellists. The perception of sour showed mean values ranging from 0.03 (panellist 'K') to 0.38 (panellist 'L'), bitter from 0.16 (panellist 'K') to 1.0 (panellist 'B'), sweet from 0.08 (panellist 'K') to 0.52 (panellist 'L') and salty from 0.1 (panellist 'K') to 0.4 (panellist 'G').

**Fig. 1**. Estimated effect of chemosensory qualities of internally applied botanical drugs that significantly influenced the probability of a drug to be also used for food (e.g., the more bitter the drug the less it is used for food). The tendency is estimated using the Bayesian logistic model and based on perceived chemosensory intensities of internally applied botanical drugs. Y axis = log-odds of use against the probability of not being used (i.e., when positive the probability of use is increased). X axis = quality intensity score (0-3). SWEE = sweet; STAR = starchy, SALT = Salty; BURN = burning/hot; BITT = Bitter ASTR = Astringent; FRUI = Fruity; NUTT = Nutty; FRES = Fresh/Cooling.

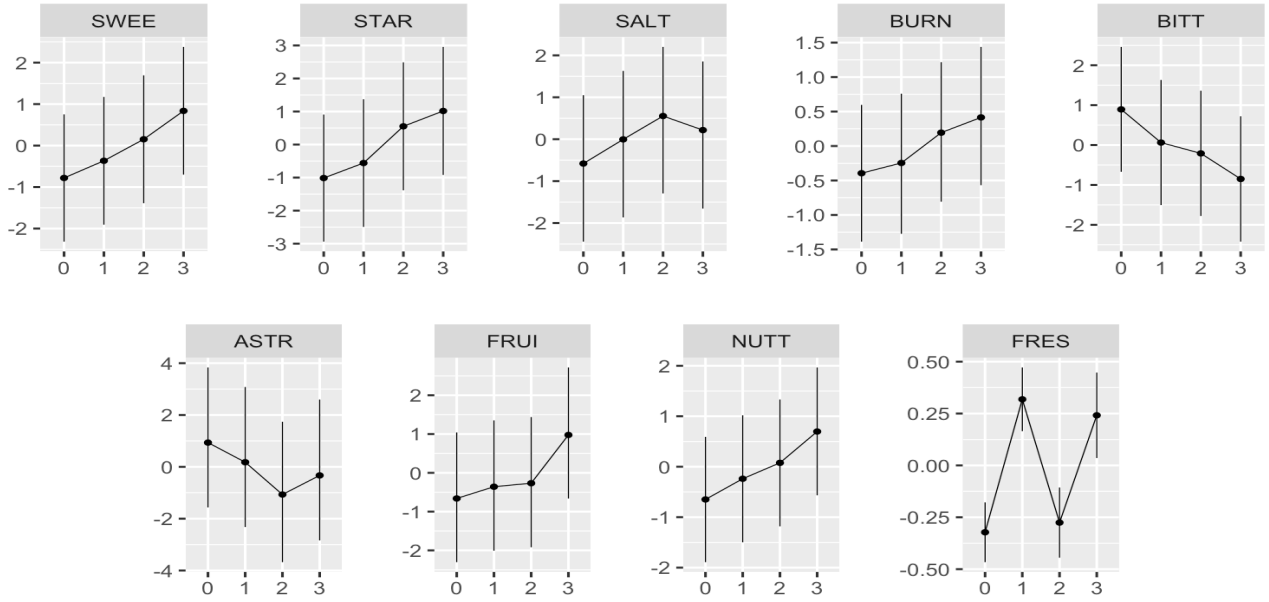



**Fig. 2.** Associations between chemosensory intensities (0-3) and frequencies of specific therapeutic uses of food drugs. Y axis = mean number of specific uses per food drug and chemosensory intensity across all drugs with intensity X for quality Y. (e.g., BITT = 3; 163 observations of bitter with an intensity score of 3 for food and non-food drugs; 13 observations of bitter with an intensity score of 3 for food drugs including 53 use records; 53/163 = 0.33). These are the observed counts (mean and 95% bootstrap c.i.) of data used to estimate values in **Fig. 1**. SWEE = sweet; STAR = starchy, SALT = Salty; BURN = burning/hot; BITT = Bitter ASTR = Astringent; FRUI = Fruity; NUTT = Nutty; FRES = Fresh/Cooling.

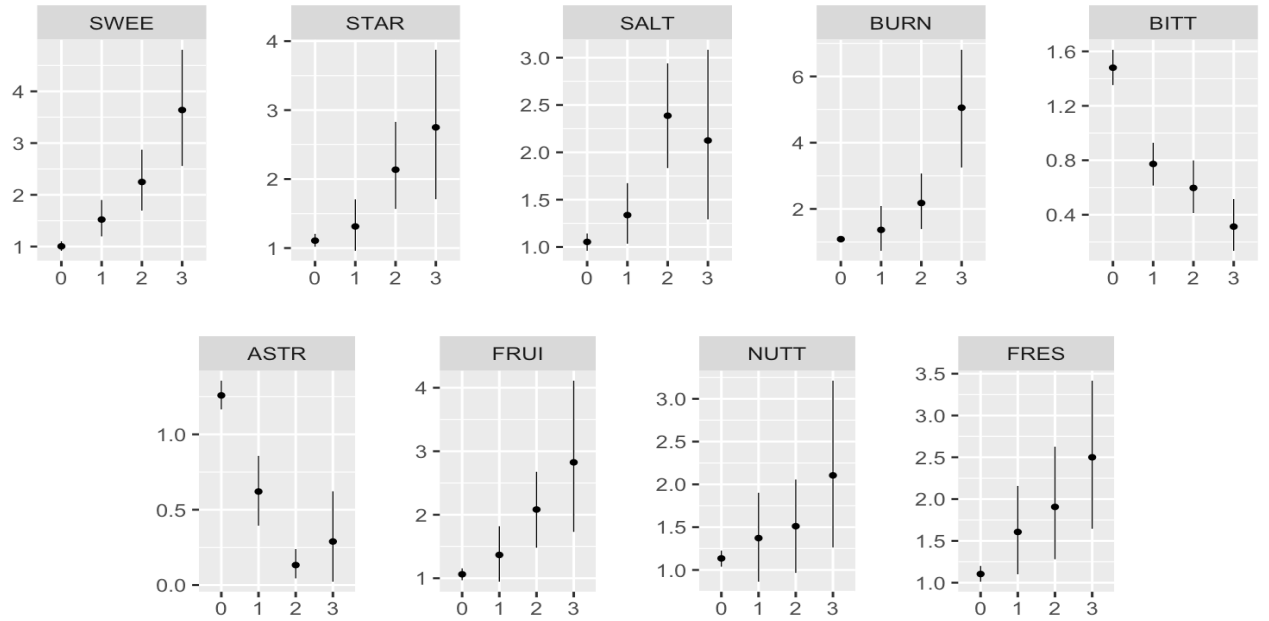


**Fig. 3**. Estimated effect of chemosensory qualities of internally applied botanical drugs that significantly influenced the probability that the drug is not used for food (e.g., the more bitter the drug the more it is used for medicine). The tendency is estimated using the Bayesian logistic model and based on perceived chemosensory intensities of internally applied botanical drugs. Y axis = log-odds of use against the probability of not being used (i.e., when positive the probability of use is increased). X axis = taste evaluations (0-3). SWEE = sweet; STAR = starchy, SALT = Salty; BURN = burning/hot; BITT = Bitter ASTR = Astringent; FRUI = Fruity; NUTT = Nutty; FRES = Fresh/Cooling.

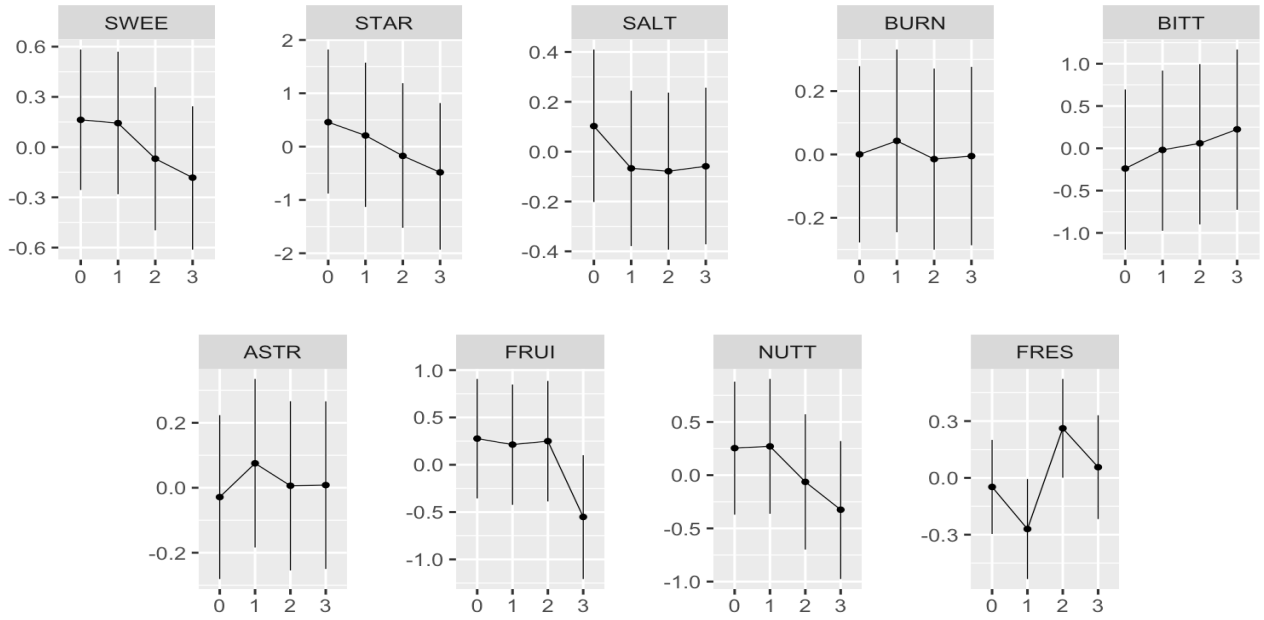
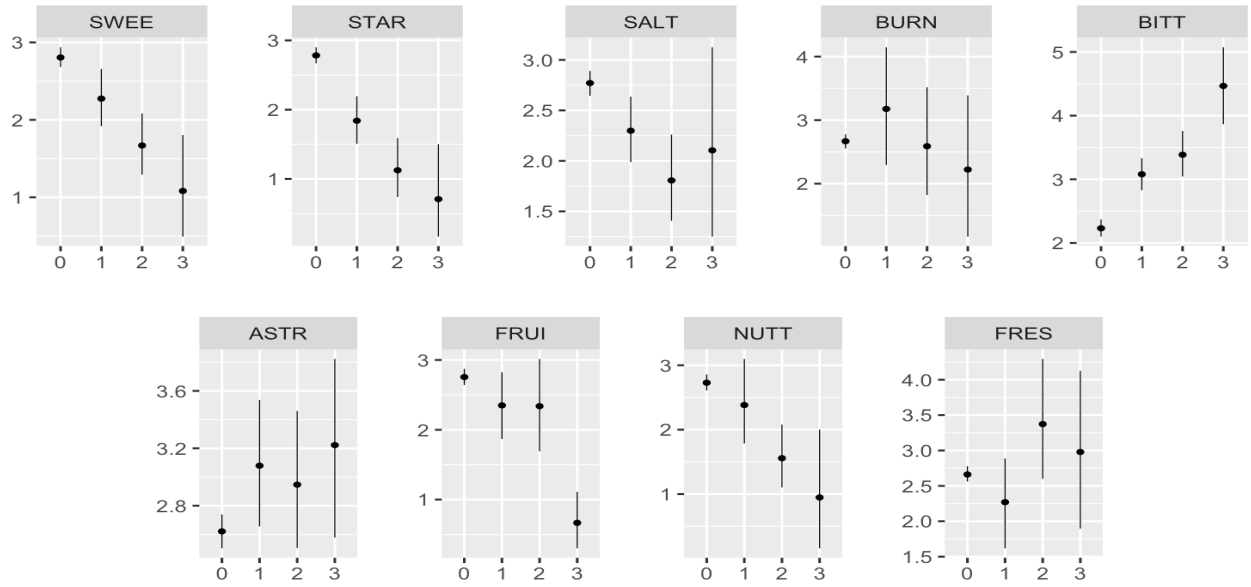



**Fig. 4.** Associations between chemosensory intensities (0-3) and frequencies of specific therapeutic uses of non-food drugs. Y axis = mean number of specific uses per non-food drug and chemosensory intensity across all drugs with intensity X for quality Y. These are the observed counts (mean and 95% bootstrap c.i.) of data used to estimate values in **Fig. 3**. SWEE = sweet; STAR = starchy, SALT = Salty; BURN = burning/hot; BITT = Bitter ASTR = Astringent; FRUI = Fruity; NUTT = Nutty; FRES = Fresh/Cooling.




### 3.2 Frequency of recorded uses, plant parts and taxonomic pattern

Food drugs showed an average of 4.3 uses per drug, while non-food drugs had an average of 3.6 uses.

**Table 1. Association of drug type (organs and derivatives) with food drugs and non-food drugs**

| | **Bark** | **Exud.** | **Flower** | **Fruit** | **Herb** | **Leaf** | **Oil** | **Seed** | **Subt.** | **Wood** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Food** | **2** | **-** | **2** | **34** | **24** | **19** | **1** | **50** | **20** | **0** |
| % | 1.3% | - | 1.3% | 22.4% | 15.8% | 12.5% | 0.7% | 32.9% | 13.2% | 0 |
| **Uses** | **15** | **-** | **10** | **109** | **107** | **93** | **5** | **213** | **96** | **0** |
| % | 2.3% | | 1.5% | 16.8% | 16.5% | 14.4% | 0.8% | 32.9% | 14.8% | 0 |
| **N-food** | **11** | **22** | **19** | **26** | **66** | **54** | **1** | **77** | **107** | **5** |
| % | 2.8% | 5.7% | 4.9% | 6.7% | 17% | 13.9% | 0.3% | 19.8% | 27.6% | 1.3% |
| **Uses** | **29** | **95** | **59** | **90** | **282** | **148** | **1** | **262** | **428** | **13** |
| % | 2.1% | 6.8% | 4.2% | 6.4% | 20% | 10.5% | 0.1% | 18.6% | 30.4% | 0.9% |

Food: plant drugs also used for food (food drugs); N-food.: plant drugs not used for food (non-food drugs); Uses: number of associated recorded therapeutic uses; Exud.: Exudate; Subt.: Subterranean part. %: Relative share.

The main plant families in terms of numbers of taxa associated with food drugs were Apiaceae (19), Rosaceae (14) Lamiaceae (11) Fabaceae (9) and Brassicaceae (8) while the main plant families associated with non-food drugs were Asteraceae (25), Apiaceae (22), Lamiaceae (18), Fabaceae (11), and Rosaceae (9).

### 3.3. Differences in therapeutic indications between food drugs and non-food drugs

Significant associations ($p < 0.005$) of therapeutic use groups were only found for non-food drugs and they were all positive (**Table 2**). They included drugs used for 'liver and jaundice', 'vaginal discharge' and 'humoral management'. Drugs used for 'uterine conditions', 'psychiatric and mood disorders' showed interesting associations with non-food drugs but were not significant.

**Table 2.** Strongest associations of therapeutic use groups with non-food drugs along with the corresponding p-values. Significant values are kept in bold.

| | |
|---|---|
| GA.LI: Gastrointestinal (Liver, jaundice) | **0,00269** |
| HMM: Humoral management | **0,00347** |
| GY.VD: Gynaecology (vaginal discharge) | **0,0035** |
| GY.UT: Gynaecology (uterine) | 0,00567 |
| NS.PS: Neurological (psychiatric) | 0,00776 |

Generally, nervous system-related and gynaecological problems were skewed towards treatments with non-food drugs including remedies for treating 'pain', 'sciatica', 'various neurological problems', drugs used as 'abortifacients and emmenagogues' and for 'various gynaecological problems' (**Table 3)**. Food drugs showed a non-significant overrepresentation with treatments for 'diarrhoeal conditions', 'gastric function', 'purgatives, laxatives, and for expelling worms', but also with the use groups 'breast and lactation', 'libido modulators', 'parasites', 'diuresis', 'other urinary conditions', as well as with 'cough' (**Table 3**).

**Table 3.** Tendency for associations of therapeutic use groups with food and non-food drugs

| Use | ANDR | ANTI | CARD | EYES | FEVE | GA.DI | GA.FU | GA.LI | GA.PL | GOUT | GY.AE | GY.BR | GY.OT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Food | 5 | 68 | 0 | 9 | 6 | 63 | 68 | **12** | 41 | 1 | 36 | 15 | 3 |
| N-food | 2 | 160 | 3 | 7 | 26 | 102 | 117 | **70** | 75 | 4 | 111 | 7 | 12 |
| **Use** | **GY.UT** | **GY.VD** | **HMM** | **LIBI** | **MOUTH** | **MU.IN** | **NOSE** | **NS.PA** | **NS.PS** | **NS.SC** | **NS.VA** | **PARA** | **RE.BD** |
| Food | **5** | **4** | **6** | 17 | 4 | 12 | 4 | 10 | 6 | 5 | 11 | 5 | 14 |
| N-food | **29** | **29** | **38** | 14 | 2 | 46 | 4 | 40 | 30 | 24 | 29 | 0 | 40 |
| **Use** | **RE.CO** | **RE.OT** | **SK.CO** | **SK.IF** | **SK.IN** | **SK.OT** | **SK.UL** | **SK.WO** | **SPLE** | **UR.CA** | **UR.DI** | **UR.OT** | **VASC** |
| Food | 59 | 14 | 1 | 4 | 1 | 0 | 0 | 1 | 11 | 9 | 76 | 40 | 2 |
| N-food | 92 | 27 | 2 | 3 | 1 | 3 | 2 | 0 | 38 | 28 | 129 | 61 | 0 |

Tendency for associations of therapeutic use groups with food and non-food drugs (N-food); orange to red: Non-food drugs; green: food drugs. Significant associations highlighted in red. ANDR: Andrology (Improve fertility, sterilization, contraceptives); ANTI: Antidotes (Bites and stings from venomous animals incl. snakes, arthropods, sea animals and remedies for envenomations, intoxications and food poisonings, applied internally); CARD: Cardiac problems (Cardiac and precordial chest pain); EYES: Eyes (Lacrimal fistula, red, watery and tired eyes, blurred vision, hordeolum, cataract); FEVE: Fever (Periodic, tertian and quartan fever, shivering (including malaria)); GA.DI: Diarrheal conditions (Diarrhoea and dysentery); GA.FU: Gastric function(Appetizers, digestives, abdominal and intestinal pain, promote digestion, heartburn, heat in the stomach, weak stomach, stomach-ache, stomach problems, hiccup, colic, flatulence, nausea, vomiting, hematemesis, intestinal ruptures, anal prolapse); GA.LI: Liver, jaundice(Liver problems and jaundice); GA.PL: Purgatives (Soften and purge the belly, purge the stomach, laxatives, emetics, drive out intestinal worms, kill intestinal worms); GOUT: Gout; GY.AE: Gynaecology (Abortifacients, uterotonics, emmenagogues, inducing delivery); GT.BR: Gynaecology (Breast: Promote lactation, induration and inflammation of the breast (mastitis)); GY.OT: Gynaecology (Other: Contraceptives, promote conception, inflamed vagina, vaginal ulcers, prevent the growth of the breasts, stop lactation); GY.UT: Gynaecology (uterine); GY.VD: Gynaecology (Staunch vaginal discharge (leucorrhoea, menstrual discharge)); HMM: Humoral management (Humoral management: purge yellow and black bile, thick humours, phlegm (watery humours), for the choleric); LIBI: Libido (Aphrodisiacs and anaphrodisiacs, prevent sexual dreams); MOUTH: Oral cavity (Problems of the teeth, gums and oral cavity: ulcers, sores, gingivitis, loose teeth hoarseness; hygiene: mouthwash, cleaning teeth); MU.IN: Musculoskeletal (Internal: Bone fractures, dislocations, injured muscles, joints and tendons, spasms, lower back pain, all sorts of bruises, for the ruptured and the spastics); NOSE: Nose (Epistaxis, polyps, purge the head from phlegm, provoke sneezing); NS.PA: Neurological (Pain: Headache, toothache, earache, stitch, unspecific pain); NS.PS: Neurological (Psychiatric: Soporifics, against melancholy and frenzy, inducing sleep and against fatigue); NS.SC: Neurological (sciatica); NS.VA: Neurological (Various: Epilepsy, tremor, paralysis, hangover, numbness, vertigo); PARA: Parasites (Lice, fleas, scabies, worms in the ear); RE.BD: Breathing difficulties (Dyspnoea, asthma); RE.CO: Cough (Catarrhs, chronic, dry and bloody cough, inflamed throat, purge chest, lungs and throat); RE.OT: Respiratory (Other: Tuberculosis, pneumonia, pleurisy, unspecific chest complaints, lost voice, lung defects, tonsillitis, diphtheria); SK.CO: Skin (Cosmetics: Hair loss, hair colouring, dandruff, nails, vitiligo, eschars, scars, freckles, clean and tighten skin, against perspiration,

armpit odour, perfumes, cosmetics); SK.IF: Skin (Infections: Inflamed wounds, erysipelas, impetigo, lepra, abscesses, furuncles, carbuncles, pustules, gangrene, paronychia, fistula, scrofula); SK.IN: Skin (Inflammation: Pruritus, dermatitis, blisters, boils, eruptions, burns, sunburns, chilblains); SK.OT: Skin (Other: Indurations and excrescences, tumours, warts, callus, swellings); SK.UL: Topical ulcer (Filthy, creeping and chronic ulcers); SK.WO: Skin (Wounds: Bleeding wounds, fissures, abrasions, splinters); SPLE: Spleen (Swollen spleen, indurations); UR.CA: Urinary (Renal and vesical calculi); UR.DI: Urinary (Diuretics: Dropsy, oedema); UR.OT: Urinary (Other: Kidney and bladder problems, urinary retention, difficult urination); VASC: Vascular (Haemorrhoids and varices).

## 4. Discussion

### 4.1. Chemosensation and uses of food drugs and non-food drugs

The relatively high variation in intensity of chemosensory perception across panellists is conditioned by polymorphisms such as those of *TAS2R*, *CD36*, *OBPIIa* as well as the gustin/CA6 genotype and differences in the salivary proteome (Hayes et al., 2008; Padiglia et al., 2010; Melis et al., 2013; 2015; Sollai et al., 2022) having implications on food preferences and intake. That sweet, starchy, fruity, and nutty tastes were positively associated with food drugs was anticipated as they indicate energy-rich sources such as sugars, starch, proteins (note that crude legume seeds were perceived as starchy) and fat (Johns, 1990, pp. 240; Chandrashekar et al., 2006; Breslin, 2013). However, the sweetest plant foods, that is, fruits, evoking relatively strong gustatory responses, provide considerably less calories than bland tasting endosperms rich in starch, fats, and proteins (Glendinning, 2022). The perception of saltiness and umami is associated with the maintenance of the electrolyte balance and the uptake of amino acids (Chandrashekar et al., 2006; Breslin, 2013). Burning/hot and cooling properties add a hedonic dimension to the overall flavour of food. Bitter and astringent metabolites are considered antifeedant compounds but like burning/hot metabolites humans learned to tolerate and include limited quantities in their diet. However, above specific and individual thresholds, bitter and astringent metabolites interfere with the perception of nutritious stimuli and mediate aversive reactions (Ganchrow et al., 1983; Johns, 1990). Food drugs were an over-average source of therapeutics used for ailments of body organs and functions directly involved in the digestion of food and the excretion of waste products including the uses associated with ‘gastric function’, ‘diarrheal conditions’, ‘purgatives’, ‘diuretics’ and ‘kidney and bladder problems, urinary retention and difficult urination’ as well as with breast feeding (‘promote lactation and inflammation of the breast’). Moreover, libido modulators and treatments for respiratory problems such as coughs, catarrhs, inflamed throat, tuberculosis, and tonsilitis showed a tendency to be sourced from food drugs contrary to the drugs used for breathing difficulties, such as asthma (**Table 3**), where beta-2 adrenergic receptor agonists, corticosteroids, anti-inflammatory and antiallergic drugs are needed.

Arguably, the daily consumption of also relatively large quantities of plant foods offered repeated possibilities for observing post-prandial effects. These effects could be best observed with relatively common health issues, where oral medication is reasonable. Treatments where also toxic (antitumor, antibacterial) effects are needed such as in the case of uterine conditions and vaginal discharge or in case of emmenagogues and abortifacients

associated with non-food drugs prevail. Also, all nervous system related problems such as remedies for treating pain, sciatica, 'various neurological problems' and 'psychiatric and mood disorders' showed a tendency to be treated with non-food drugs (**Table 3**) because neuroactive metabolites and strong pharmacologic effects are generally not sought through diet.

Fruits and seeds are important sources of food drugs, while subterranean organs are important sources of non-food drugs (**Table 2**). The nutritional, digestible, textural, and chemical differences between these botanical drug types explain part of the different taste qualities perceived. The differences among the five most important plant families in terms of number of species used are the Brassicaceae, used as an important source of food drugs and the Asteraceae, constituting an important source of non-food drugs. The sequence of plant families with the highest number of orally applied non-food drugs parallels that of identified medicinally used taxa recorded in *DMM* in general (considering all uses), which were Asteraceae (46), Apiaceae (44), Lamiaceae (36), Fabaceae (27) and Rosaceae (20) (Staub et al., 2016) and distinguishes from the food-drugs by a relatively low importance of the Brassicaceae and high importance of Asteraceae (**Table 1**).

The higher versatility of food drugs (4.3 uses per drug) with respect to orally applied non-food drugs (3.6 uses per drug) is probably due to their frequent consumption and broad geographical distribution and use, which allowed for multiple observations and knowledge exchange of post-ingestive physiological effects on a large scale (see also Martins et al., 2019 and Leonti et al., 2020).

### 4.2. Salty food drugs

Salts have their own salty taste and, moreover, enhance flavour by suppressing bitterness (Breslin and Beauchamp, 1997). This gustatory relation and the perceived saltiness and savoury taste of food drugs found here seems to accentuate the relative low perception of bitterness and permits (in addition to adding salt or any other bitter masking tastant to a dish prepared with bitter tasting plant parts) that bitter tasting metabolites implicated in disease prevention, are ingested in health-relevant amounts. Especially wild gathered and bitter Asteraceae and Brassicaceae leafy vegetables are reported as traditional healthy foods (e.g., Heldreich, 1862; Pieroni et al., 2002; Leonti et al., 2006; Dogan, 2012; Łuczaj and Dolina, 2015; Geraci et al., 2018; Pieroni et al., 2023) and known to contain chemopreventive and anti-inflammatory bitter-tasting sesquiterpene lactones, glucosinolates, and flavonoids (Mithen, 2006; Crozier et al., 2006; Chadwick et al., 2013).

The average scores for both, bitter and salty across all considered Brassicaceae and Asteraceae leafy food drugs included in this study were in fact considerably above (*vide infra*) the mean values for all food drugs together which were 0.31 for bitter and 0.37 for salty. As a comparison, the mean values for bitter and salty of the non-food plant drugs were 0.75 and 0.18, respectively (**Supplementary Tables 3 and 4**) while all non-food drugs perceived as bitter (scored between 1 and 3; mean intensity: 1,65) showed a mean value for salty of 0.14 and all food drugs perceived as bitter (mean intensity: 1.46) showed a mean value for salty of 0.39. The Brassicaceae food-drugs obtained from shortpod mustard (*Hirschfeldia incana*), watercress (*Nasturtium officinale*), rocket (*Eruca vesicaria*), cress (*Lepidium sativum*), turnip (*Brassica rapa*) and cabbage (*Brassica oleracea*) showed a mean value of 0.57 for bitter and of 0.61 for salty while the average values for the Asteraceae leafy food drugs (sow thistle, (*Sonchus oleraceus*), chicory (*Cichorium intybus*), lettuce and prickly lettuce (*Lactuca sativa* and *L. serriola*)) were 1.18 for bitter and 0.65 for salty.

Salty food drugs (summed up intensity for salty taste across all trials divided by number of individual trials $\geq 1$)[2] were indicated for problems related to excretion and retention of fluids such as faeces, urine, menstrual blood, bronchial discharge, and, also as emetics (**Supplementary Tables 2 and 4**). Generally, salty drugs were associated with treatments for diarrhoea and laxatives (Leonti et al., 2024). However, contrary to the negative association observed between overall salty drugs with urinary retention in Leonti et al. (2024) salty food drugs were favourably used as diuretics (see footnote 2). The presence of hot and pungent tasting metabolites (*vide infra*) in several food drugs perceived concomitantly as salty explains this apparently discordant association.

### 4.3. Hot and cooling food drugs: urinary retention and galactagogues

[2]*Morus* fruits were recommended for catarrhs and diarrhoea (summed up intensity for salty taste across all trials: 9/ number of trials: 7), *Trigonella foenum-graecum* seeds for dysentery and rectal prolapse, (4/4), roots of *Raphanus raphanistrum* for intoxications with poisonous fungi, for lubricating the belly and inducing menstruation, as an expectorant and diuretic (14/10), the herb of *Portulaca oleracea* as an antidote, for bladder and kidney problems for the stomach (6/5), the herb of *Asparagus* sp. as a diuretic and for kidney and stomach problems (10/5), leaves of *Sonchus* sp. for the stomach and lactation, (7/5), the fruit of *Lagenaria siceraria* for the stomach and as a laxative (7/5), the herb of *Scandix* sp. for the kidney, bladder, liver and as a diuretic (5/5), the leaves of *Allium ampeloprasum* as an antidote, diuretic and for purging the trachea and the chest (9/5), the bulbs of *Allium sativum* as a diuretic antidote, for intestinal worms and parasites, for treating cough and haemorrhoids (10/4), the bulbs of *Allium sphaerocephalon* for diarrhoea and as a diuretic (6/4), the leaves of *Apium graveolens* and *Helosciadium nodiflorum* as an antidote, diuretic, emetic, for diarrhoea, stomach problems, breast inflammation (9/5) and (13/6), respectively, the roots of *Helosciadium nodiflorum* as an antidote, emetic and for diarrhoea (7/5), the fruits of *Levisticum officinale* as an antidote, diuretic and for gastrointestinal problems (4/4), the roots of *Brassica rapa* as an aphrodisiac, (10/6), the herb of *Atriplex hortensis* as a bland laxative (10/5), the fruit of *Cucumis sativus* for the stomach and bladder (7/4) and the herb of *Daucus carota* for the bladder and as a diuretic (5/5).

The interaction of spicy plant metabolites with ion channels of the transient receptor potential (TRP) family can mediate burning and hot sensations as well as cold and refreshing stimuli (Roper, 2014). Besides thermosensation, TRP channels expressed in the gastrointestinal tract are also involved in mechanosensation, gastrointestinal motility, pain, and hyperalgesia as well as in the absorption of nutrients and secretion of mucus and fluids (Holzer, 2011). Alterations in TRP channel expressions and functions are implicated in a range of disorders affecting the digestive system and, therefore, modulation of TRP channel functioning limited to the alimentary tract, are seen as possible therapeutic strategies (Holzer, 2011). Since TRPV1-knockout mice urinate more frequently than wild type-mice and do so without voiding their bladder (Birder et al., 2002), TRPV receptor interaction likely explains the association of hot tasting food drugs with treatment of urinary retention, incontinence, kidney, and bladder problems (see also Leonti et al., 2024). Hot tasting metabolites occurring in food drugs interacting with thermosensitive TRPV1 or and TRPA1 include oleocanthal, thymol, carvacrol, cinnamaldehyde, allicin and allyl isothiocyanate (Macpherson et al., 2005; 2007; Lee et al., 2008; Peyrot des Gachons et al., 2011). Oleocanthal is found in olive oil, which was indicated for abdominal pain and for expelling intestinal worms in Antiquity (**Supplementary Table 2**). Thymol is a component of the aerial parts of thyme species (*Thymus* spp.; indicated for abdominal pain, hematemesis and as diuretics), present in fruits of wild cumin (*Lagoecia cuminoides*; indicated for abdominal pain, flatulence, hiccup, as a diuretic and for haematuria) and in aerial parts of oregano and marjoram (*Origanum* spp.; indicated for abdominal pain, dropsy, urination problems, purging black bile and inducing vomiting). Carvacrol is present in the aerial parts of thyme species and the arial parts of conehead thyme (*Thymbra capitata*; indicated for driving out intestinal worms and phlegm as well as a diuretic) but also in the aerial parts of *Origanum* spp. (see above for indications). Cinnamaldehyde is present in the bark of wild cinnamon (*Neolitsea cassia*; recommended as a diuretic and in case of renal weakness) and cinnamon (*Cinnamomum* sp.; recommended for urinary retention, dropsy, as a diuretic and for kidney diseases). Allyl isothiocyanate is a metabolite of the herb of black mustard (*Brassica nigra*; indicated as a diuretic), the herb of cabbage (indicated as a diuretic, for digestion and softening the belly but also for stopping diarrhoea) and the root of wild radish (*Raphanus raphanistrum*; indicated for lubricating the belly, as a diuretic and for treating cough and phlegm). Allicin is present in garlic (*Allium sativum*) and other *Allium* spp. (for uses see footnote 2).

Cooling sensations can be mediated by menthol, geraniol and eucalyptol interacting with TRPM8 (Behrendt et al., 2004). However, several compounds naturally occurring in spices

and food (e.g., menthol, cinnamaldehyde, allyl isothiocyanate or camphor) show promiscuous and, also reversed agonist/antagonist relationships with a range of thermo-sensitive TRP channels including TRPV1 and TRPV3 (Macpherson et al., 2006; Everaerts et al., 2011). We found remedies for ‘breast and lactation’ recommended in *DMM* skewed towards the food group (**Table 3**), a result also reflected by the large share of food drugs among galactagogues noted on a global scale (Sibeko and Johns, 2021). In our database drugs for ‘breast and lactation’ include Apiaceae drugs such as dill and fennel fruits as well as leaves and fruits of anis. The essential oils of anis and fennel fruits are rich in *trans*-anethole (80-95% and up to 80%, respectively; Bruneton, 1999) which has spasmolytic and bacteriostatic properties (Wichtl, 2002, p. 82). The essential oil of dill herb contains above all α-phellandrene, β-phellandrene, and 3,9-oxy-*p*-menth-l-ene (90-97%) while dill seed oil contains foremost carvone and dihydrocarvone (68-83%) (Charles et al., 1995). Liposoluble components such as *trans*-anethole and carvone are passed on via food and breastmilk to the new-born (Hausner et al., 2008). *trans*-Anethol, described as fresh and cooling interacts in an agonistic way with TRPA1, but instead of inducing nociception such as capsaicin it desensitizes the receptor leading to analgesic effects (Memon et al., 2019). L-carvone is an antagonist of TRPM8 and mediates a cooling sensation (Bandell et al., 2007). Galactagogues such as fennel, anis, and dill fruits, containing *trans*-anethole and L-carvone might thus convey soothing effects to sore and inflamed nipples during lactation and, due to the spasmolytic and bacteriostatic properties of *trans*-anethol, help with gastric pain and colics of the new-born. The moderate spasmolytic and bacteriostatic properties of essential oil components may ultimately improve the absorption of nutrients and positively influence weight gain of the new-born. However, there is limited data on the effect on the duration of breastfeeding, weight gain and milk volume by the administration of botanical drugs used as galactagogues in general (Foong et al., 2020). The term ‘galactagogue' might thus effectively describe a drug with multiple perceived beneficial effects, for the mother and the infant, in the context of breast feeding. Other food drugs indicated specifically as galactagogues were the fruits of the chaste tree (*Vitex agnus-castus*), barley grain (*Hordeum vulgare*), the seeds of chickpea (*Cicer arietinum*), fava bean (*Vicia faba*) and black cumin (*Nigella sativa*) and the leaves of sow thistle, lettuce, and basil (*Ocimum basilicum*). The recommendation of using chaste tree fruits in *DMM* for promoting lactation stands in sharp contrast with the dopaminergic prolactin-suppressive properties of *V. agnus-castus* constituents and modern phytotherapeutic uses (Wuttke et al., 2003). While a link between low milk production and low prolactin levels is confirmed, it is not clear whether this is a

causal factor in all women with low milk production (Brodribb, 2018). Non-food drugs used for 'breast and lactation' are the roots of Mediterranean saltbush (*Atriplex halimus*), common mallow (*Malva sylvestris*), bryony (*Bryonia cretica*) and pale bugloss (*Echium italicum*) as well as the herb of poppy anemone (*Anemone coronaria*) and veeny milkwort (*Polygala venulose*) and the seeds of pale bugloss. The hypothesis that latex bearing plant species are preferentially used as galactagogues (Bingel and Farnsworth, 1994) is difficult to sustain with our data as the only taxa bearing latex and recommended also as galactagogues are *L. sativa* and *S. oleraceus* (**Supplementary Table 2**).

### 4.4 Bitter plant drugs

Since at least Greco-Roman times bitter gets associated with medicine and disease. Bitter taste was considered a cue for inherent medicinal qualities (Totelin, 2018b; Baker, 2018) and Aristoteles (ca. 383-322 BCE) noted that bitter moisture humidifies the tongues of the sick making them taste everything bitter (Aristoteles, 1931). The detection and rejection of bitter and sour foods has also been associated with the avoidance of spoiled foods and toxins (Glendinning, 1994; Lindemann, 2001; Breslin, 2013). Yet, a correlation between bitter tasting compounds and toxicity is difficult to establish because not all bitter compounds are toxic at a nutritionally relevant dose and not all toxins are bitter (Glendinning, 1994; Nissim et al., 2017). Still, the avoidance of pharmacologically active metabolites is probably the reason why many pharmaceutical drugs taste bitter (Johns, 1990; Mennella et al., 2013). Contemporary applications of bitter drugs are directed towards the induction of salivary flow, gastric juices, bile, and pancreatic juice and for stimulating the motor function of the stomach and the small intestine in case of dyspeptic disorders, anismus (contractions of the rectum), lack of appetite and for augmenting the tone of the gastrointestinal muscles (Wagner et al., 2007, p. 55-58). Bitter taste receptors in the gastrointestinal tract are implicated in the modification of gut hormone release indicating a therapeutic potential in case of metabolic diseases (Rozengurt, 2006; Kok et al., 2018).

Remedies for 'liver and jaundice' and 'humoral management' were significantly associated with bitter taste and non-food drugs (**Table 3**) including uses for purging and resolving bitter bile, resonating with the choleretics and cholekinetics of today. However, many of the non-food drugs indicated for humoral management are highly toxic and were used because of their toxicity related laxative and emetic effects (Leonti et al., 2024). These drugs are now largely excluded from herbal medicine including the seeds of castor bean (*Ricinus communis*) which contain the toxic alkaloid ricinine and highly toxic polypeptide toxins, such

as the infamous ricin, provoking amongst other symptoms bloody diarrhoea (Dewick, 2002). Seeds of common corncockle (*Agrostemma githago*) contain toxic triterpene saponines and type I ribosome-inactivating proteins, acting in a similar way to ricin from castor bean (Weise et al., 2020). The genus *Daphne*, (here: seeds and leaves of flax-leaved daphne (*D. gnidium*) and leaves of olive daphne (*D. oleoides*)) is known for its toxic diterpenes (e.g., daphnetoxin) and diterpene esters (e.g., mezerein). Daphnetoxin and its derivatives have been obtained from the areal parts of *D. gnidium* (Vidal et al., 2012) and *D. oleoides* (Yeşilada et al., 2001). The highly toxic phorbol ester mezerein, concentrated in the seeds of *Daphne* species, has vesicatory properties, and induces bloody diarrhoea (Falbe and Regitz, 1997; Wink, 2015). The essential oil of pennyroyal (*Mentha pulegium*) contains high concentrations of the monoterpene pulegone which is metabolized to toxic electrophilic intermediates readily forming adducts with proteins (Dewick, 2002), whereas hellebores (*Helleborus* species) contain cardioactive bufadienolides (Dewick, 2002) while false hellebores (*Veratrum* species) bear teratogenic steroidal alkaloids (Dewick, 2002; Zagler et al., 2005; Schep et al., 2006). The fruit of colocynth (*Citrullus colocynthis*) and the fruit juice of squirting cucumber (*Ecballium elaterium*) are known as powerful cathartics containing irritant and cytotoxic cucurbitacins causing bloody diarrhoea (Yesilada et al., 1988; Greige-Gerges et al., 2007; Javadzadeh et al., 2013). The latex of many spurge species (*Euphorbia* spp.) contains toxic diterpene esters with irritant effects on the skin and the mucosa causing cell-proliferation and tumour progression (Dewick, 2002) while the root and root-resin of scammony (*Convolvulus scammonia*) contain cathartic glycosides (resin glycosides) (Noda et al., 1990).

Also, non-food drugs used for liver problems were sourced from several toxic species, though to a lesser extent when compared to those used for humoral management. Squill bulbs (*Drimia maritima*) are rich in cardioactive bufadienolides and intoxication causes vomiting (Dewick, 2002). Sea daffodil bulbs (*Pancratium maritimum*) contain galanthamine, crinine, lycorine, and other cytotoxic and emetic alkaloids (Berkov et al., 2004; Dewick, 2002). The essential oil of sweet flag (*Acorus calamus*) is rich in asarone isomers implicated in cardiotoxicity, hepatotoxicity, reproductive toxicity, mutagenicity, and carcinogenicity (Uebel et al., 2021). Therefore, the directive on flavourings (88/388/EEC) set the maximum levels of β-asarone to 0.1 mg/kg in foodstuffs and to 1 mg/kg in alcoholic beverages (SCF, 2002). Phytotherapeutic preparations containing extracts of greater celandine (*Chelidonium majus*) are still on the European market, but related hepatotoxic adverse effects have resulted in a set safety threshold of maximally 2.5. mg total *Chelidonia* alkaloid intake per

day (EMA/HMPC/369801/2009, 2011; Teschke et al., 2011). Remarkably, the bitter herb of artichoke (*Cynara cardunculus*) used today for its liver protecting properties and metabolic diseases such as dyslipidaemia (Wichtl, 2002; Bundy et al., 2008) was apparently not recommended for any systemic medical application in *DMM*.

### 4.5 Astringency and the relation with food

Polyphenols and tannins are antimicrobial and antifeedant plant defense metabolites producing a sensation of astringency in the oral cavity of mammal herbivores, reducing taste perception as well as the digestion and absorption of nutritious metabolites. Astringency is a tactile sensation mediated by the trigeminal nerve (Green, 1993; Schöbel et al., 2014) and caused by covalent and non-covalent interactions of polyphenols with proteins of the mucous membranes and salivary enzymes. The protein-linking capacity of tannic agents leads to the formation of a protective precipitate and coagulated proteins of the membranes resulting in attenuated stimuli, reduced inflammation and reduced secretion of water and electrolytes (Wagner et al., 2007; Schöbel et al., 2014). Reduced peristalsis and constipating effects are useful for treating diarrhoea (Wagner et al., 2007 p. 117) but the astringent effects interfere with digestion and absorption of nutrients.

It is thought that the proline and histidine-rich tannin precipitating proteins occurring in saliva have evolved as a defense line against tannin intoxication by tannin rich foods occurring in (unripe) fruits, leaves, nuts, and roots (Bennick, 2002). Fruits change their chemistry and pharmacologic properties during maturation. Unripe fruits are often astringent due to the presence of proanthocyanidins (condensed tannins) which during maturation polymerize and precipitate (Goldstein and Swain, 1963). The state of maturation when recommending the fruits of quince (*Cydonia oblonga*), apple (*Malus domestica*), pear (*Pyrus communis*), azarole (*Crataegus azarolus*), lote tree (*Celtis australis*), cornel (*Cornus mas*), plums (*Prunus domestica*), wild cherry (*Prunus avium*) and mulberry (*Morus* sp.) for diarrheal conditions was not specified in *DMM*. Probably, in various cases, the use of semi-mature fruits or varieties with astringent qualities was implied because in fruits, the concentration of free sugars such as fructose, alditols and disaccharides with moderate laxative properties augments with ongoing maturation (Allen, 1932; Ravich et al., 1983; Wagner et al., 2007). However, in *DMM* only a few edible fruits are recommended concomitantly for diarrhoea as well as laxatives (those of wild cherry and of emmer wheat (*Triticum turgidum* subsp. *dicoccum*)) or for diarrhoea as well as for driving out intestinal worms (apples). The only

fruits recommended as laxatives but not for diarrhoeal conditions were figs (*Ficus carica*) and those of bottle gourd (*Lagenaria siceraria*).

### 4.6. Libido regulators and food

Libido regulators were dominated by food drugs (**Table 3**), which might be a hint at the origin of this therapeutical concept. Green leafy vegetables were generally regarded as “cooling” and anaphrodisiac remedies (Ferrand, 1990; Avicenna, 2014, pp. 1194–1195) while spicy and hot vegetables containing metabolites such as glucosinolates and allyl-sulphates as libido stimulating foods (Kline, 2001; Leonti and Casu, 2018). Food drugs recorded in *DMM* said to stimulate libido are the seeds of turnip (*B. rapa*), rocket (*E. vesicaria*), cress (*L. sativum*), flax seeds (*Linum usitatissimum*), the fruits of anis, the green parts of rocket, cress, wild leek (*Allium ampeloprasum*), peppermint (*Mentha* × *piperita*) as well as the underground organs of species such as dragon lily (*Dracunculus vulgaris*), cuckoopint (*Arum maculatum*), tassel hyacinth (*Leopoldia comos*a) and carrots (*Daucus carota*) with apparencies reminiscent of phalluses, vulvas and testicles. The herb of common purslane (*Portulaca oleracea*) was indicated for reducing libido.

Non-food drugs reported to stimulate libido were the underground parts of costus (*Aucklandia costus*), spring sowbread (*Cyclamen repandum*), common sword-lily (*Gladiolus italicus*), mandrake (*Mandragora officinarum*), lady's bedstraw (*Galium verum*), the leaves of navelwort (*Umbilicus rupestris*), the fruit of the turpentine tree (*Pistacia terebinthus*) and the seeds of annual clary (*Salvia viridis*). Seeds of lettuce and prickly lettuce (*L. sativa* and *L. serriola*) as well as the root of white waterlily (*Nymphaea alb*a) were recommended for reducing libido. The chemistry of the seeds of both lettuce species is poorly studied but the latex (lactucarium or lettuce-opium), which was used to adulterate opium, contains the guaianolide sesquiterpene lactones lactucin and lactucopicrin which have shown analgesic and sedative effects in mice (Chadwick et al., 2013; Wesołowska et al., 2006). Lactucarium was still included in the 1934 British Pharmaceutical Codex where it is said to have a taste like opium and was indicated as a sedative for irritable cough (The British Pharmaceutical Codex, 1934, p. 584). The roots of the white waterlily were recommended for preventing wet dreams. Quinolizidine alkaloids were identified in *N. alba* (Wróbel, 1967; Emboden, 1981) while from the dotleaf waterlily (*N. ampla*) aporphine, which is closely related to the dopamine receptor agonist ampomorphine, was obtained (Emboden, 1981; Bertol et al., 2004). Apomorphine is used for treating erectile dysfunction and Parkinson’s disease but

since it is also a potent emetic, antiemetics need to be co-administrated, in order, to control vomiting (Brayfield, 2017).

## 5. Conclusion

Therapeutics used for ailments of body organs directly involved in the digestion of food and the excretion of waste products showed a tendency to be sourced from food. All staple crops and most fruits and vegetables cultivated or collected from the wild were used as therapeutics suggesting that physiologic and pharmacologic consequences of food intake, was an important factor in the development of traditional medicine. The observation and comprehension of post-prandial effects of plant foods on body functions together with their widespread use and low toxicity led to a relatively high diversification of therapeutic uses. Botanical drugs also used for food are perceived as having starchy, sweet, fruity, nutty, salty, burning/hot, and cooling tastes and low intensities of bitter and astringent tastes. Although food drugs were negatively associated with bitterness, bitter and concomitantly salty tasting vegetables (Asteraceae and Brassicaceae) form a group of bitter and salty/umami food drugs with a higher mean score for bitterness (Asteraceae) than the average score for bitterness of non-food drugs. Comprehensively, the differences in taste qualities between food drugs and non-food drugs here compared are demarcating the organoleptic requirements of foods rather than those of medicine.

Botanical drugs used for ‘liver and jaundice’, ‘vaginal discharge’ and ‘humoral management’ were negatively associated with food and, also drugs for uterine conditions and psychiatric disorders showed a tendency for having been sourced from non-food drugs in ancient Greek-Roman medicine. The significant association of non-food drugs with liver problems and jaundice was not expected. The significant association of therapeutics used for humoral management with the non-food group is related to the induction of drastic physiologic effects such as vomiting and diarrhoea and suggests that this concept has been a relatively newer therapeutic concept in medical history.

The tasting panel tried exclusively dried plant materials (drugs), which do, especially in case of food, not always reflect real-life applications. Using fresh plant material when indicated, might thus be a reasonable way for obtaining more relevant data. Yet, we argue that the whole profile of experimentally assessed taste qualities should be used for the determination of gustatory plant selection criteria. We conclude that systematic comparisons of therapeutic uses of food and non-food drugs and comparing their experimentally assessed chemosensory qualities offer possibilities for understanding the co-evolutionary

development of empiric and traditional medicines. In allegory to Exodus 12:8 and the seminal book by Timothy Johns “With bitter herbs they shall eat it” (1990; now: “the Origins of Human Diet and Medicine” we might add a bit of salt to this meme so that that ‘with bitter *and* salty herbs they shall it’.

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**Supplementary Table A. The 219 herbal drug aggregates included in the Ph. Eur. 9.5 (2017) Latin index with botanical origin (*s.l.*). Scientific names and main synonyms of the plant taxa are according to www.theplantlist.org. Eur. = Native European distribution count. Drugs with food history highlighted in grey.**

| Drug | Species | Native distribution |
|---|---|---|
| *Absinthii herba* | *Artemisia absinthium* L. | EURASIA + AFRICA (N) |
| *Acaciae gummi, Acaciae gummi dispersione desiccatum* | *Acacia senegal* (L.) Willd.; *Acacia seyal* Delile, *Acacia* spp. | ASIA (W) |
| *Acanthopanacis gracilistyli cortex* | *Eleutherococcus nodiflorus* (Dunn) S.Y.Hu. | ASIA |
| *Agni casti fructus* | *Vitex agnus-castus* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Agrimoniae herba* | *Agrimonia eupatoria* L. | EURASIA + AFRICA (N) |
| *Akebiae caulis* | *Akebia quinata* (Houtt.) Decne.; *Akebia trifoliata* (Thunb.) Koidz. | ASIA |
| *Alchemillae herba* | *Achemilla vulgaris* L. *sensu latiore* | EUROPE |
| *Allii sativi bulbi pulvis* | *Allium sativum* L. | ASIA |
| *Aloe barbadensis* | *Aloe vera* (L.) Burm.f. | AFRICA |
| *Aloe capensis* | *Aloe ferox* Mill., *Aloe* spp. | AFRICA |
| *Althaeae folium, Althaeae radix* | *Althaea officinalis* L. | EUROPE + AFRICA (N)+ ASIA (W) |
| *Amomi fructus, Amomi fructus rotundus* | *Amomum compactum* Sol. ex Maton | ASIA |
| *Amygdalae oleum raffinatum, Amygdalae oleum virginale* | *Prunus dulcis* (Mill.) D.A. Webb var. *dulcis* or *Prunus dulcis* (Mill.) D.A. Webb var. *amara* (DC.) Buchheim | EUROPE + AFRICA (N) + ASIA (SW) |
| *Andrographidis herba* | *Andrographis paniculata* (Burm.f.) Nees | ASIA |
| *Anemarrhenae asphodeloides rhizoma* | *Anemarrhena asphodeloides* Bunge | ASIA |
| *Angelicae archangelicae radix* | *Angelica archangelica* L. | EURASIA + GREENLAND |
| *Angelicae dahuricae radix* | *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav. | ASIA |
| *Angelicae pubescentis radix* | *Angelica pubescens* Maxim. | ASIA |
| *Angelicae sinensis radix* | *Angelica sinensis* (Oliv.) Diels | ASIA |
| *Anisi aetheroleum, Anisi fructus* | *Pimpinella anisum* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Anisi stellati fructus* | *Illicium verum* Hook.f. | ASIA |
| *Arachidis oleum hydrogenatum, Arachidis oleum raffinatum* | *Arachis hypogaea* L. | AMERICA (S) |
| *Arnicae flos, Arnicae tinctura* | *Arnica montana* L. | EUROPE |

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| *Atractylodis lanceae rizoma* | *Atractylodes lancea* (Thunb.) DC. (*Atractylodes chinensis* (DC.) Koidz.) | ASIA |
| *Atractylodis macrocephalae rizoma* | *Atractylodes macrocephala* Koidz. | ASIA |
| *Aucklandiae radix* | *Aucklandia lappa* DC. | ASIA |
| *Aurantii amari epicarpium et mesocarpium, Aurantii amari flos, Aurantii amari epicarpii et mesocarpii tinctura* | *Citrus × aurantium* L. | ASIA |
| *Aurantii dulcis aetheroleum, Neroli aetheroleum* | *Citrus sinensis* (L.) Osbeck (*Citrus aurantium* L. var. *dulcis* L.) | ASIA |
| *Ballotae nigrae herba* | *Ballota nigra* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Balsamum peruvianum* | *Myroxylon balsamum* (L.) Harms var. *perierae* (Royle) Harms | AMERICA (M, S) |
| *Balsamum tolutanum* | *Myroxylon balsamum* (L.) Harms var. *balsamum* | AMERICA (M, S) |
| *Belamcandae chinensis rhizoma* | *Iris domestica* (L.) Goldblatt & Mabb. | ASIA |
| *Belladonnae folium, Belladonnae pulvis normatus, Belladonnae folii extractum siccum normatum, Belladonnae folii tinctura normata* | *Atropa belladonna* L. | EURASIA + AFRICA (N) |
| *Benzoe sumatranus, Benzois sumatrani tinctura* | *Styrax benzoin* Dryand., *Styrax parallelonеurum* Perkins | ASIA (SE) |
| *Benzoe tonkinensis, Benzois tonkinensis tinctura* | *Styrax tonkinensis* Craib ex Hartwich | ASIA (SE) |
| *Betulae folium* | *Betula pendula* Roth., *Betula pubescens* Ehrh. | EURASIA |
| *Bistortae rhizoma* | *Persicaria bistorta* (L.) Samp. (*Polygonum bistorta* L.) | NORTHERN HEMISPHERE |
| *Boldi folium, Boldi folii extractum siccum* | *Peumus boldus* Molina | AMERICA (S) |
| *Boraginis officinalis oleum raffinatum* | *Borago officinalis* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Bupleuri radix* | *Bupleurum chinense* DC., *Bupleurum scorzonerifolium* Willd. | ASIA |
| *Calendulae flos* | *Calendula officinalis* L. | EUROPE |
| *Camelliae sinensis non fermentata folia* | *Camellia sinensis* (L.) Kuntze | ASIA |
| *Capsici fructus, Capsici extractum spissum normatum, Capsici oleoresina raffinata et normata, Capsici tinctura normata* | *Capsicum annuum* L. var. *minimum* (Mill.) Heiser and *Capsicum frutescens* L. | AMERICA (M) |

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| *Carthami flos, Carthami oleum raffinatum* | *Carthamus tinctorius* L. | ASIA (SW) |
| *Carvi fructus, Carvi aetheroleum* | *Carum carvi* L. | EURASIA |
| *Caryophylli flos, Caryophylli floris aetheroleum* | *Syzygium aromaticum* (L.) Merill et L. M. Perry (*Eugenia caryophyllus* (C. Spreng.) Bull. et Harr.) | ASIA (SE) |
| *Centaurii herba* | *Centaurium erythraea* Rafn s. l. including *C. majus* (H. et L.) Zeltner and *C. suffruticosum* (Griseb.) Ronn. (syn. : *Erythraea centaurium* Persoon; *C. umbellatum* Gilibert ; C. *minus* Gars.). | EURASIA |
| *Centellae asiaticae herba* | *Centella asiatica* (L.) Urb. | ASIA |
| *Chamomillae romanae flos* | *Chamaemelum nobile* (L.) All. (*Anthemis nobilis* L.). | EUROPE |
| *Chelidonii herba* | *Chelidonium majus* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Cimicifugae rhizoma* | *Cimicifuga racemosa* (L.) Nutt. | AMERICA (N) |
| *Cinchonae cortex, Cinchonae extractum fluidum normatum* | *Cinchona pubescens* Vahl (*Cinchona succirubra* Pav.), *Cinchona calisaya* Wedd., *Cinchona ledgeriana* Moens ex Trimen | AMERICA (S) |
| *Cinnamomi cassiae aetheroleum* | *Cinnamomum cassia* (L.) J.Presl | ASIA |
| *Cinnamomi cortex, Cinnamomi zeylanici corticis aetheroleum, Cinnamomi zeylanici folii aetheroleum* | *Cinnamomum zeylanicum* Nees (*C. verum* J.Presl.) | ASIA |
| *Citri reticulatae epicarpium et mesocarpium, Citri reticulatae aetheroleum* | *Citrus reticulata* Blanco. | ASIA |
| *Citronellae aetheroleum* | *Cymbopogon winterianus* Jowitt ex Bor | ASIA |
| *Cocois oleum raffinatum* | *Cocos nucifera* L. | TROPICS |
| *Codonopsidis radix* | *Codonopsis pilosula* (Franch.) Nannf. | ASIA |
| *Coicis semen* | *Coix lacryma-jobi* L. var. *mayuen* (Roman.) Stapf | ASIA |
| *Colae semen* | *Cola nitida* (Vent.) Schott et Endl. (C. vera K. Schum.), *Cola acuminata* (P. Beauv.) Schott et Endl. (*Sterculia acuminata* P. Beauv.). | AFRICA |
| *Colophonium* | *Pinus* spp. | UNDEFINED |
| *Coptidis rhizoma* | *Coptis chinensis* Franch., *Coptis deltoidea* C.Y. Cheng | ASIA |

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| | et Hsiao, *Coptis japonica* (Thunb.) Makino | |
| *Coriandri fructus, Coriandri aetheroleum* | *Coriandrum sativum* L. | ASIA (SW) |
| *Crataegi folium cum flore, Crataegi fructus, Crataegi folii cum flore extractum fluidum quantificatum, Crataegi folii cum flore extractum siccum* | *Crataegus monogyna* Jacq., *C. laevigata* (Poir.) DC. (*C. oxyacanthoides* Thuill.; *C. oxyacantha* auct.), *Crataegus* spp. | EUROPE + AFRICA (N)+ ASIA (W) |
| *Curcumae longae rhizoma* | *Curcuma longa* L. | ASIA |
| *Curcumae zanthorrhizae rhizoma* | *Curcuma xanthorrhiza* Roxb. (*C. xanthorrhiza* D. Dietrich). | ASIA (SE) |
| *Cyamopsidis seminis pulvis, Guar galactomannanum* | *Cyamopsis tetragonoloba* (L.) Taub. | ASIA |
| *Cynarae folium, Cynarae folii extractum siccum* | *Cynara scolymus* L. | EUROPE |
| *Digitalis purpureae folium* | *Digitalis purpurea* L. | EUROPE + AFRICA (N) |
| *Dioscoreae nipponicae rhizoma* | *Dioscorea nipponica* Makino | ASIA |
| *Dioscoreae oppositifoliae rhizoma* | *Dioscorea oppositifolia* L. | ASIA |
| *Drynariae rhizoma* | *Drynaria fortunei* (Kunze ex Mett.) J.Sm. | ASIA |
| *Echinaceae angustifoliae radix* | *Echinacea angustifolia* DC. | AMERICA (N) |
| *Echinaceae pallidae radix* | *Echinacea pallida* (Nutt.) Nutt. | AMERICA (N) |
| *Echinaceae purpureae herba, Echinaceae purpureae radix* | *Echinacea purpurea* (L.) Moench. | AMERICA (N) |
| *Ecliptae herba* | *Eclipta prostrata* (L.) L. | TROPICS |
| *Eleutherococci radix* | *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim. | ASIA |
| *Ephedrae herba* | *Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk et C.A.Mey., *Ephedra equisetina* Bunge | ASIA |
| *Equiseti herba* | *Equisetum arvense* L. | NORTHERN HEMISPHERE |
| *Eucalypti folium, Eucalypti aetheroleum* | *Eucalyptus globulus* Labill. | AUSTRALIA |
| *Eucommiae cortex* | *Eucommia ulmoides* Oliv. | ASIA |
| *Fagopyri herba* | *Fagopyrum esculentum* Moench. | ASIA |
| *Filipendulae ulmariae herba* | *Filipendula ulmaria* (L.) Maxim. (*Spiraea ulmaria* L.). | EURASIA |
| *Foeniculi amari fructus, Foeniculi amari fructus aetheroleum, Foeniculi amari herbae aetheroleum, Foeniculi dulcis fructus* | *Foeniculum vulgare* Mill. ssp. *vulgare* var. *vulgare*. | EUROPE + AFRICA (N) + ASIA (CW) |

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| *Frangulae cortex, Frangulae corticis extractum siccum normatum* | *Rhamnus frangula* L. (*Frangula alnus* Miller). | EURASIA + AFRICA (N) |
| *Fraxini folium* | *Fraxinus excelsior* L., *Fraxinus oxyphylla* M. Bieb. | EUROPE + AFRICA (N) |
| *Fraxini rhynchophyllae cortex* | *Fraxinus chinensis* Roxb. (*Fraxinus szaboana* Lingelsh.),*Fraxinus stylosa* Lingelsh | ASIA |
| *Fumariae herba* | *Fumaria officinalis* L. | EUROPE |
| *Gardeniae fructus* | *Gardenia jasminoides* J.Ellis | ASIA |
| *Gentianae radix, Gentianae tinctura* | *Gentiana lutea* L. | EUROPE + ASIA (W) |
| *Ginkgonis folium, Ginkgonis extractum siccum raffinatum et quantificatum* | *Ginkgo biloba* L. | ASIA (SE) |
| *Ginseng radix, Ginseng extractum siccum* | *Panax ginseng* C. A. Meyer. | ASIA |
| *Gossypii oleum hydrogenatum* | *Gossypium hirsutum* L., *Gossypium* spp. | AMERICA (M) |
| *Graminis rhizoma* | *Agropyron repens* (L.) Beauv. (*Elymus repens* (L.) Gould) | NORTHERN HEMISPHERE |
| *Guaranae semen* | *Paulinia cupana* Kunth | AMERICA (S) |
| *Hamamelidis cortex, Hamamelidis folium* | *Hamamelis virginiana* L. | AMERICA (N) |
| *Harpagophyti radix, Harpagophyti extractum siccum* | *Harpagophytum procumbens* DC., *Harpagophytum zeyheri* Decne. | AFRICA |
| *Hederae folium* | *Hedera helix* L. | EUROPE |
| *Helianthi annui oleum raffinatum* | *Helianthus annuus* L. | AMERICA (M,N) |
| *Hibisci sabdariffae flos* | *Hibiscus sabdariffa* L. | AFRICA |
| *Hippocastani semen, Hippocastani seminis extractum siccum normatum* | *Aesculus hippocastanum* L. | EUROPE |
| *Houttuyniae herba* | *Houttuynia cordata* Thunb. | ASIA (SE) |
| *Hydrastis rhizoma* | *Hydrastis canadensis* L. | AMERICA (N) |
| *Hyperici herba, Hyperici herbae extractum siccum quantificatum* | *Hypericum perforatum* L. | EURASIA + AFRICA (N) |
| *Ipecacuanhae radix, Ipecacuanhae extractum fluidum normatum, Ipecacuanhae pulvis normatus, Ipecacuanhae tinctura normata* | *Cephaelis ipecacuanha* (Brot.) A. Rich., *Cephaelis acuminata* H.Karst. | AMERICA (S) |
| *Isatidis radix* | *Isatis tinctoria* L. | ASIA |
| *Juniperi galbulus, Juniperi aetheroleum* | *Juniperus communis* L. | NORTHERN HEMISPHERE |
| *Lavandulae flos, Lavandulae aetheroleum* | *Lavandula angustifolia* Mill. | EUROPE |
| *Leonuri cardiacae herba* | *Leonurus cardiaca* L. | EURASIA |
| *Levistici radix* | *Levisticum officinale* W.D.J.Koch | EUROPE + ASIA (SW) |

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| *Lichen islandicus* | *Cetraria islandica* (L.) Acharius s.l. | NORTHERN HEMISPHERE |
| *Ligustici chuanxiong rhizoma* | *Ligusticum striatum* DC. (*Ligusticum chuanxiong* S.H.Qiu, Y.Q.Zeng, K.Y.Pan, Y.C.Tang & J.M.Xu) | ASIA |
| *Limonis aetheroleum* | *Citrus limon* (L.) Osbeck | ASIA |
| *Lini semen, Lini oleum virginale* | *Linum usitatissimum* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Liquiritiae radix, Liquiritiae extractum siccum ad saporandum* | *Glycyrrhiza glabra* L., *Glycyrrhiza inflata* Batalin, *Glycyrrhiza uralensis* Fisch. | EUROPE + AFRICA (N) + ASIA (CW) |
| *Lupuli flos* | *Humulus lupulus* L. | NORTHERN HEMISPHERE |
| *Lycii fructus* | *Lycium barbarum* L. | EURASIA |
| *Lycopi herba* | *Lycopus lucidus* Turcz. ex Benth. | ASIA |
| *Lythri herba* | *Lythrum salicaria* L. | NORTHERN HEMISPHERE |
| *Magnoliae biondii flos immaturus* | *Magnolia biondii* Pamp. (*Yulania biondii* (Pamp.) D.L.Fu) | ASIA |
| *Magnoliae officinalis cortex* | *Magnolia officinalis* Rehder & E.H.Wilson | ASIA |
| *Magnoliae officinalis flos* | *Magnolia officinalis* Rehder & E.H.Wilson | ASIA |
| *Malvae folium* | *Malva sylvestris* L., *Malva neglecta* Wallr. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Malvae sylvestris flos* | *Malva sylvestris* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Marrubii herba* | *Marrubium vulgare* L. | EUROPE + AFRICA (N) |
| *Mastix* | *Pistacia lentiscus* L. var. *latifolius* Coss. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Mate folium* | *Ilex paraguariensis* A.St.-Hil. | AMERICA (S) |
| *Matricariae flos, Matricariae extractum fluidum, Matricariae aetheroleum* | *Matricaria chamomilla* L. (*Matricaria recutita* L., *Chamomilla recutita* (L.) Rauschert)) | EURASIA |
| *Melaleucae aetheroleum, Niaouli typo cineolo aetheroleum* | *Melaleuca alternifolia* (Maiden and Betch) Cheel, *M. linariifolia* Sm., *M. dissitiflora* F. Muell. | AUSTRALIA |
| *Meliloti herba* | *Melilotus officinalis* (L.) Pall. | EURASIA + AFRICA (N) |
| *Melissae folium, Melissae folii extractum siccum* | *Melissa officinalis* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Menthae arvensis aetheroleum partim mentholum depletum* | *Mentha canadensis* L. (*M. arvensis* L. var. *glabrata* (Benth) Fern., *M. arvensis* | NORTHERN HEMISPHERE |

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| | var. *piperascens* Malinv. ex Holmes) | |
| *Menthae piperitae folium, Menthae piperitae aetheroleum, Menthae piperitae folii extractum siccum* | *Mentha ×piperita* L. | EUROPE + ASIA (SW) |
| *Menyanthidis trifoliatae folium* | *Menyanthes trifoliata* L. | NORTHERN HEMISPHERE |
| *Millefolii herba* | *Achillea millefolium* L. | NORTHERN HEMISPHERE |
| *Myristicae fragrantis aetheroleum* | *Myristica fragrans* Houtt. | ASIA |
| *Myrrha, Myrrhae tinctura* | *Commiphora molmol* Engler, *Commiphora* spp. | ASIA (W) |
| *Myrtilli fructus recens, Myrtilli fructus recentis extractum siccum raffinatum et normatum, Myrtilli fructus siccus* | *Vaccinium myrtillus* L. | NORTHERN HEMISPHERE |
| *Notoginseng radix* | *Panax pseudoginseng* Wall. var. *notoginseng* (Burk.) Hoo et Tseng (*Panax notoginseng* (Burk.) F.H. Chen ex C.Y. Wu et K.M. Feng) | ASIA |
| *Oenotherae oleum raffinatum* | *Oenothera biennis* L., *Oenothera lamarckiana* L. | AMERICA (N) |
| *Oleae folium, Oleae folii extractum siccum, Olea herbaria, Olivae oleum raffinatum, Olivae oleum virginale* | *Olea europaea* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Olibanum indicum* | *Boswellia serrata* Roxb. ex Colebr. | ASIA |
| *Ononidis radix* | *Ononis spinosa* L. | EUROPE + AFRICA (N)+ ASIA (W) |
| *Opium crudum, Opii extractum siccum normatum, Opii pulvis normatus, Opii tinctura normata* | *Papaver somniferum* L. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Origani herba* | *Origanum onites* L., *Origanum vulgare* L. subsp. *hirtum* (Link) Ietsw. | EUROPE |
| *Paeoniae radix alba* | *Paeonia lactiflora* Pall. | ASIA |
| *Paeoniae radix rubra* | *Paeonia lactiflora* Pall., *Paeonia veitchii* Lynch | ASIA |
| *Papaveris rhoeados flos* | *Papaver rhoeas* L. | EURASIA + AFRICA (N) |
| *Passiflorae herba, Passiflorae herbae extractumsiccum* | *Passiflora incarnata* L. | AMERICA (S) |
| *Pelargonii radix* | *Pelargonium sidoides* DC., *Pelargonium reniforme* Curt. | AFRICA |
| *Persicariae tinctoriae folium* | *Persicaria tinctoria* (Aiton) H.Gross (*Polygonum tinctorium* Aiton) | EURASIA |

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| *Pini pumilionis aetheroleum* | *Pinus mugo* Turra | EUROPE |
| *Pini sylvestris aetheroleum* | *Pinus sylvestris* L. | EURASIA |
| *Piperis fructus* | *Piper nigrum* L. | ASIA |
| *Piperis longi fructus* | *Piper longum* L. | ASIA |
| *Plantaginis lanceolatae folium* | *Plantago lanceolata* L. s.l. | EURASIA |
| *Plantaginis ovatae semen, Plantaginis ovatae seminis tegumentum* | *Plantago ovata* Forssk. (*P. ispaghula* Roxb.). | EURASIA + AFRICA (N) |
| *Polygalae radix* | *Polygala senega* L., *Polygala* spp. | AMERICA (N) |
| *Polygoni avicularis herba* | *Polygonum aviculare* L. | NORTHERN HEMISPHERE |
| *Polygoni cuspidati rhizoma et radix* | *Polygonum cuspidatum* Sieb. et Zucc. | ASIA |
| *Polygoni multiflori radix* | *Polygonum multiflorum* Thunb. | ASIA |
| *Polygoni orientalis fructus* | *Polygonum orientale* L. | ASIA |
| *Primulae radix* | *Primula veris* L., *Primula elatior* (L.) Hill. | EURASIA |
| *Prunellae spica* | *Prunella vulgaris* L. | EURASIA + AFRICA (N) |
| *Pruni africanae cortex* | *Prunus africana* (Hook f.) Kalkm. (*Pygeum africanum* Hook f.). | AFRICA |
| *Psyllii semen* | *Plantago afra* L. (*Plantago psyllium* L.), *Plantago indica* L. (*Plantago arenaria* Waldstein and Kitaibel) | EURASIA + AFRICA (N) |
| *Puerariae lobatae radix* | *Pueraria montana* var. *lobata* (Willd.) Sanjappa & Pradeep | ASIA |
| *Puerariae thomsonii radix* | *Pueraria montana* var. *chinensis* (Ohwi) Sanjappa & Pradeep | ASIA |
| *Quercus cortex* | *Quercus robur* L., *Q. petraea* (Matt.) Liebl., *Q. pubescens* Willd. | EUROPE + ASIA (W) |
| *Quillajae cortex* | *Quillaja saponaria* Molina | AMERICA (S) |
| *Rapae oleum raffinatum* | *Brassica napus* L., *Brassica campestris* L. | ASIA |
| *Ratanhiae radix, Ratanhiae tinctura* | *Krameria triandra* Ruiz and Pavon | AMERICA (M,S) |
| *Rhamni purshianae cortex, Rhamni purshianae extractum siccum normatum* | *Rhamnus purshiana* DC. (*Frangula purshiana* (D.C.) A. Gray ex J. C. Cooper) | AMERICA (N) |
| *Rhei radix* | *Rheum palmatum* L., *Rheum officinale* Baill. | ASIA |
| *Ribis nigri folium* | *Ribes nigrum* L. | EURASIA |
| *Ricini oleum virginale, Ricini oleum raffinatum, Ricini oleum hydrogenatum* | *Ricinus communis* L. | AFRICA |

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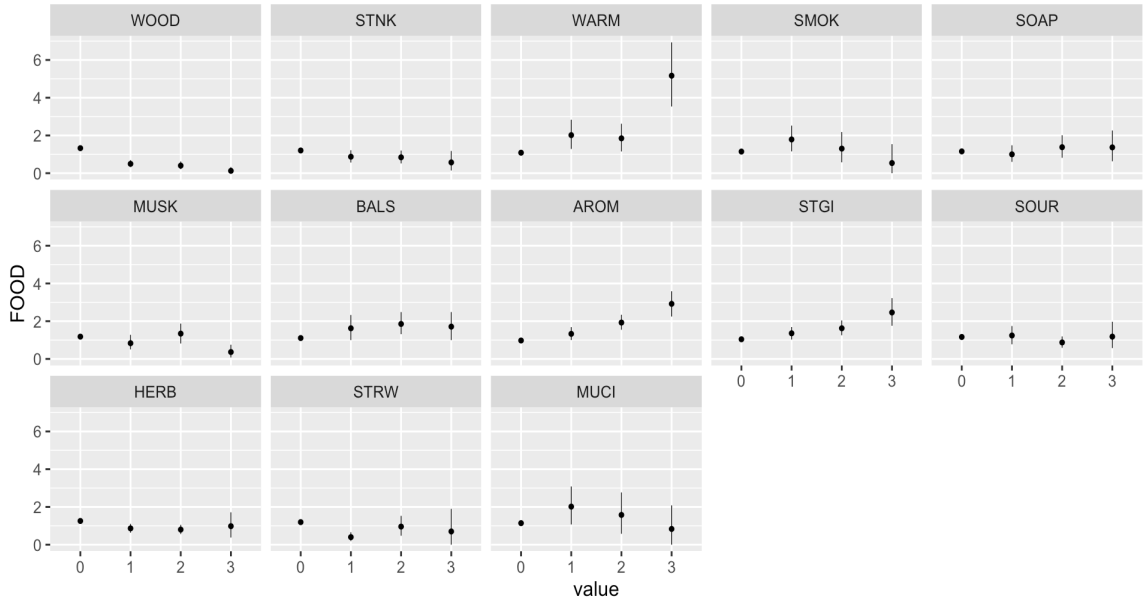
| *Rosae pseudo-fructus* | *Rosa canina* L., *R. pendulina* L., *Rosa* spp. | EURASIA |
| *Rosmarini folium, Rosmarini aetheroleum* | *Rosmarinus officinalis* L. | EUROPE + AFRICA (N) |
| *Rusci rhizoma* | *Ruscus aculeatus* L. | EUROPE + AFRICA (N) |
| *Sabalis serrulatae fructus, Sabalis serrulatae extractum* | *Serenoa repens* (W.Bartram) Small. (*Sabal serrulata* (Michaux) Nichols). | AMERICA (N) |
| *Salicis cortex, Salicis corticis extractum siccum* | *Salix purpurea* L., *S. daphnoides* Vill., *S. fragilis* L., *Salix* spp. | EUROPE + AFRICA (N) + ASIA (SW) |
| *Salviae lavandulifoliae aetheroleum* | *Salvia lavandulifolia* Vahl | EUROPE + AFRICA (N) |
| *Salviae miltiorrhizae radix et rhizoma* | *Salvia miltiorrhiza* Bunge | ASIA |
| *Salviae officinalis folium, Salviae tinctura* | *Salvia officinalis* L. | EUROPE |
| *Salviae sclareae aetheroleum* | *Salvia sclarea* L. | EURASIA + AFRICA (N) |
| *Salviae trilobae folium* | *Salvia fructicosa* Mill. (*S. triloba* L. fil). | EURASIA + AFRICA (N) |
| *Sambuci flos* | *Sambucus nigra* L. | EUROPE + AMERICA (N) |
| *Sanguisorbae radix* | *Sanguisorba officinalis* L. | NORTHERN HEMISPHERE |
| *Schisandrae chinensis fructus* | *Schisandra chinensis* (Turcz.) Baill. | ASIA |
| *Scutellariae baicalensis radix* | *Scutellaria baicalensis* Georgi | ASIA |
| *Sennae folium, Sennae folii extractum siccum normatum, Sennae fructus acutifoliae, Sennae fructus angustifoliae* | *Cassia senna* L. (*C. acutifolia* Delile), *Cassia angustifolia* Vahl | AFRICA |
| *Serpylli herba* | *Thymus serpyllum* L.s.l. | EUROPE + AFRICA (N) |
| *Sesami oleum raffinatum* | *Sesamum indicum* L. | ASIA |
| *Silybi mariani fructus, Silybi mariani extractum siccum raffinatum et normatum* | *Silybum marianum* (L.) Gaertn. | EURASIA |
| *Soiae oleum hydrogenatum, Soiae oleum raffinatum* | *Glycine max* (L.) Merr. (*G. hispida* (Moench) Maxim.) | ASIA |
| *Solidaginis herba* | *Solidago gigantea* Aiton, *Solidago canadensis* L. | AMERICA (N) |
| *Solidaginis virgaureae herba* | *Solidago virgaurea* L. | EUROPE |
| *Sophorae japonicae flos, Sophorae japonicae flos immaturus* | *Styphnolobium japonicum* (L.) Schott | ASIA |
| *Spicae aetheroleum* | *Lavandula latifolia* Medik. | EUROPE |
| *Stramonii folium, Stramonii pulvis normatus* | *Datura stramonium* L. | AMERICA (M,N) |

| | | |
|---|---|---|
| *Tanaceti parthenii herba* | *Tanacetum parthenium* (L.) Sch.Bip. | EURASIA |
| *Taraxaci officinalis herba cum radice, Taraxaci officinalis radix* | *Taraxacum officinale* F.H. Wigg. | TEMPERATE REGIONS |
| *Terebinthinae aetheroleum* | *Pinus pinaster* Aiton | EUROPE + AFRICA (N) |
| *Thymi herba, Thymi typo thymolo aetheroleum* | *Thymus vulgaris* L., *Thymus zygis* L. | EUROPE + AFRICA (N) |
| *Tiliae flos* | *Tilia cordata* Mill., *Tilia platyphyllos* Scop., *Tilia* × *europaea* L. | EURASIA |
| *Tormentillae rhizoma, Tormentillae tinctura* | *Potentilla erecta* (L.) Raeusch. (*P. tormentilla* Stokes) | EURASIA |
| *Tragacantha* | *Astragalus gummifer* Labill., *Astragalus* spp. | ASIA |
| *Trigonellae foenugraeci semen* | *Trigonella foenum-graecum* L. | ASIA |
| *Tritici aestivi oleum raffinatum, Tritici aestivi oleum virginale* | *Triticum aestivum* L. | ASIA (W) |
| *Uncariae rhynchophyllae ramulus cum uncis* | *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. | ASIA |
| *Urticae folium, Urticae radix* | *Urtica dioica* L., *Urtica urens* L. | TEMPERATE REGIONS |
| *Uvae ursi folium* | *Arctostaphylos uva-ursi* (L.) Spreng. | NORTHERN HEMISPHERE |
| *Valerianae radix, Valerianae extractum aquosum siccum, Valerianae extractum hydroalcoholicum siccum, Valerianae radix minutata, Valerianae tinctura* | *Valeriana officinalis* L. s.l. | EURASIA |
| *Verbasci flos* | *Verbascum thapsus* L., *V. densiflorum* Bertol. (*V. thapsiforme* Schrad), *V. phlomoides* L. | EURASIA |
| *Verbenae citriodorae folium* | *Aloysia citriodora* Palau (*A. triphylla* (L'Hér.) Kuntze; *Verbena triphylla* L'Hér.; *Lippia citriodora* Kunth.) | AMERICA (S) |
| *Verbenae herba* | *Verbena officinalis* L. | EURASIA + AFRICA (N) |
| *Violae herba cum flore* | *Viola arvensis* Murray, *Viola tricolor* L. | EURASIA + AFRICA (N) |
| *Zanthoxyli bungeani pericarpium* | *Zanthoxylum bungeanum* Maxim. | ASIA |
| *Zingiberis rhizoma* | *Zingiber officinale* Roscoe | ASIA |

**Supplementary Fig. 1**. Associations between taste intensities (0-3) and frequencies of specific therapeutic uses of food drugs (non-significant effects). Y axis = mean number of specific uses per food drug and chemosensory intensity across all drugs with intensity X for quality Y. These are the observed counts (mean and 95% bootstrap c.i.) of data used to estimate values in the Bayesian logistic model. Warming, aromatic and pungent chemosensory qualities show positive tendencies while woody, stinky and smoky qualities show negative tendencies. WOOD: Woody; STNK: Stinky; WARM: Warming; SMOK: Smoky; SOAP: Soapy; MUSK: Musky; BALS: Balsamic; AROM: Aromatic; STGI: Stinging/Mustardy (pungent); SOUR: Sour; HERB: Herby/Leafy; STRW: Straw-like; MUCI: Mucilaginous.



**Supplementary Fig. 2.** Associations between taste intensities (0-3) and frequencies of specific therapeutic uses of orally applied plant drugs not used for food (non-significant effects). Y axis = mean number of specific uses per non-food drug and chemosensory intensity across all drugs with intensity X for quality Y. These are the observed counts (mean and 95% bootstrap c.i.) of data used to estimate values in the Bayesian logistic model. WOOD: Woody; STNK: Stinky; WARM: Warming; SMOK: Smoky; SOAP: Soapy; MUSK: Musky; BALS: Balsamic; AROM: Aromatic; STGI: Stinging/Mustardy (pungent); SOUR: Sour; HERB: Herby/Leafy; STRW: Straw-like; MUCI: Mucilaginous.