Taste shaped the use of botanical drugs

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Abstract

The perception of taste and flavour (a combination of taste, smell and chemesthesis) here also referred to as chemosensation, enables animals to find high-value foods and avoid toxins. Humans have learned to use unpalatable and toxic substances as medicines, yet the importance of chemosensation in this process is poorly understood. Here we generate tasting-panel data for botanical drugs and apply phylogenetic generalised linear mixed models to test whether intensity and complexity of chemosensory qualities as well as particular tastes and flavours can predict ancient Graeco-Roman drug use. We found chemosensation to be strongly predictive of

therapeutic use: botanical drugs with high therapeutic versatility have simple yet intense tastes and flavours, and 21 of 22 chemosensory qualities predicted at least one therapeutic use. In addition to the common notion of bitter tasting medicines, we also found starchy, musky, sweet, cooling, and soapy drugs associated with versatility. In ancient Greece and Rome, illness was thought to arise from imbalance in bodily fluids or humours, yet our study suggests that uses of drugs were based on observed physiological effects that are often consistent with modern understanding of chemesthesis and taste receptor pharmacology.

Introduction

'A bitter pill to swallow' is just one of many common idioms referring to the taste of medicine, which from ancient to early modern times has relied mostly on botanical drugs (Touwaide, 2022). In ancient Greece and Rome, the expected effects of botanical drugs were explained by their taste (Jones, 1959; Einarson and Link, 1990; Jouanna and Allies, 2012) and according to the prevailing medical theory, disease resulted from a disequilibrium between bodily fluids or humours including phlegm, blood, yellow bile and black bile; drugs affected the flow and balance of these humours (Jones, 1959; King, 2013). Theophrastus (300 BCE) attributed sweet the capacity to smoothen, astringent with the power to desiccate and solidify, pungent with the capacity to cut or to separate out the heat, salty with desiccating and irritating properties, and bitter with the capacity to melt and irritate (Einarson and Link, 1990). Other systems of medicine, such as Ayurveda and Traditional Chinese Medicine continue to classify *materia medica* according to tastes and flavours (Dragos and Gilca, 2018; Shou-zhong, 2018), and indigenous societies use chemosensory qualities to select botanical drugs (Casagrande, 2000; Leonti et al., 2002; Shepard, 2004).

The perception of taste and flavour (a combination of taste, smell and chemesthesis) here also referred to as chemosensation, has evolved to meet nutritional requirements and are particularly important in omnivores for seeking out nutrients and avoiding toxins (Rozin and Todd, 2016; Breslin, 2013; Glendinning, 2022). The rejection of bitter stimuli has generally been associated with the avoidance of toxins (Glendinning, 1994; Lindemann, 2001; Breslin, 2013) but to date no clear relationship between bitter compounds and toxicity at a nutritionally relevant dose could be established (Glendinning, 1994; Nissim et al., 2017). While bitter tasting metabolites occurring in fruits and vegetables have been linked with a lower risk for contracting cancer and cardiovascular diseases (Drewnoswski and Gomez-Carneros, 2000), the avoidance of pharmacologically active compounds is probably the reason why many medicines, including botanical drugs, taste bitter (Johns, 1990; Mennella et al., 2013).

Botanical drugs are chemically complex and often used for a range of different health problems (Wagner et al., 2007). Chemical complexity determines pharmacological complexity, since different chemicals interact with different targets (Gertsch, 2011), and influence taste complexity and intensity (Spence and Wang, 2018; Breslin and Beauchamp, 1997; Green et al., 2010). Today, some associations between chemosensory qualities and therapeutic uses, such as bitter tasting botanical drugs for stomach problems or astringent ones for diarrhoea, are still recognised in Western herbal medicine (Wagner et al., 2007). These observations establish a role for chemosensory qualities in medicine. Yet, taste and flavour are largely irrelevant to modern medicine, aside from the pharmaceutical industry looking for ways to mask bad tastes (Mennella et al., 2013).

Whether ancient systems of traditional medicine could be relevant to modern science is questionable. The theory of humours was the principal underlying concept of Western

medicine from ancient Graeco-Roman times until the Industrial Age, but as an entirely discredited theory it might be expected that associated practices also lack scientific basis. However, we propose that taste and flavour perception of botanical drugs links humoral theory to modern medicine. We hypothesize that chemosensation and underlying physiological effects mediated by chemesthesis and taste receptor pharmacology co-explain the diversity of therapeutic uses of botanical drugs in ancient times. We further hypothesize that associations between perceived complexity and intensity of chemosensory qualities of botanical drugs and their versatility (number of categories of therapeutic use a botanical drug is used for) provide insights into the development of empirical pharmacological knowledge and therapeutic behaviour. If tastes and flavours, as determined by a modern-day tasting panel, do predict uses as recorded in ancient texts, this would be an unprecedented insight into how chemosensation was translated into physiological and therapeutic expectations and how it guided human behaviour in pre-scientific times. To test these hypotheses, we assessed the relationships between chemosensory qualities, their intensity and complexity with therapeutic uses of botanical drugs described in Pedanios Dioscorides' pharmacognostic compendium, *De Materia Medica* (*DMM*; Matthioli, 1967-1970; Staub et al., 2016), the foremost pharmaceutical source of antiquity. *DMM* compiles knowledge on the sourcing, preparation and therapeutic uses of botanical drugs traded and used in the Eastern Mediterranean region of the Roman Empire during the 1st century CE (Riddle, 1985). We collected 700 botanical drugs described in *DMM*, (**Supplementary file 1**) and used quality descriptors to represent chemosensation by a trained tasting panel scoring each botanical drug for presence and intensity of each quality (**Figure 1; Supplementary files 2 and 3**). We arranged the botanical drugs into therapeutic uses according to affected organs, therapeutic functions, diseases, and symptoms as indicated in *DMM*, and into broader and more inclusive categories of therapeutic use (**Figure 1; Supplementary files 1 and 4**). By applying

phylogenetic generalised linear mixed models (PGLMMs) to our data and a plant phylogeny (Zanne et al., 2014; see Methods) we tested whether perceived taste and flavour qualities, as well as their overall intensity and complexity predict recorded therapeutic uses whilst simultaneously accounting for the confounding effects of the shared uses and chemosensory stimuli by drugs from closely related species.

Results

Diversity of chemosensory qualities and therapeutic uses

We used 22 descriptors to represent perceived chemosensory qualities of 700 botanical drugs and identified 46 therapeutic uses across 25 categories as described in *DMM* (**Figure 1; Supplementary files 1 and 4**). A group of eleven panellists conducted 3973 sensory trials (see Methods) and reported 10,463 individual perceptions of qualities. The most frequently reported qualities were bitter (1556 reports; 39% of all assessed samples), herby/leafy (1146 reports; 29%), aromatic (795 reports; 20%) and stinging (730 reports; 18%), while the least was mucilaginous (128 reports; 3.2%). Weak qualities were most frequently reported (5244 reports; 50%); 3899 (37%) of reports were of medium strength and 1320 (13%) were perceived as strong. Balsamic (69 reports; 24%), burning/hot (41 reports; 22%) and fresh/cooling (49 reports; 21%) were the qualities most often perceived as strong, while smoky (87 reports; 61%), sour (224 reports; 60%) and starchy (190 reports; 59%) the qualities most often perceived as weak. Panellists perceived between zero (e.g., *Anemone coronaria*, root) and ten (*Cinnamomum verum*, bark) individual qualities per drug. The mean number of therapeutic uses per botanical drug was 6.3 and the most frequently mentioned therapeutic use being ‘gynaecology – abortion and menses’ (272 use records) and the least frequently mentioned ‘cardiac problems’ (seven use records).

Simple and intense chemosensory perception is associated with therapeutic versatility

The relationship between intensity of chemosensation (the sum of all chemosensory scores across all qualities, **Figure 2A**; see Methods) and therapeutic versatility is positive (p_x < 0.001; **Figure 2C**). On the other hand, chemosensory complexity (the number of taste and flavour qualities a botanical drug is scored for, **Figure 2B**; see Methods) is negatively associated with how many different out of the 25 categories of therapeutic use botanical drugs are used for (e.g., cardiac, gynaecological, humoral, henceforth referred to as 'therapeutic versatility' (p_x = 0.026; **Figure 2D**). Importantly, the multiple regression framework we use allows for each trait to covary whilst simultaneously predicting their underlying relationship with therapeutic versatility.

Strength of specific chemosensory qualities predict therapeutic versatility

All models we analyse have strong phylogenetic signal (modal h^2 > 0.9, see Methods) which may have led to misleading impressions about medicinal tastes and flavours in the past in analyses which did not account for such statistical non-independence. Indeed, while we do find a significant positive association between the strength of bitterness and therapeutic versatility (p_x = 0.013), the most versatile drugs were not only the bitter-tasting ones; contrary to popular concepts of bad-tasting medicine (Mennella et al., 2013). We also find that the perceived strengths of starchy (p_x = 0.017), musky (p_x = 0.013), sweet (p_x = <0.018), and soapy (p_x = 0.002) qualities were positively associated with therapeutic versatility while the intensity of perceived sourness was negatively associated with versatility (p_x = <0.001).

Associations between specific chemosensory qualities and specific uses

All therapeutic uses (with the exception of 'gynaecology – other') are significantly associated with at least one specific chemosensory quality, whether positively (99 instances) or

negatively (50 instances) and often with high magnitude of effect (**Figure 3; Supplementary file 5**). Thus, the perceived presence or absence of several specific qualities significantly confer the chemosensory perception of medicine (less than 5% of their estimated parameter distribution crosses zero, p_x <0.05) with high magnitude of effect (**Figure 3**).

Discussion

Unexpectedly, botanical drugs eliciting fewer but intense chemosensations were more versatile (**Figure 2**). People often associate complexity with intensity, and taste complexity is popularly interpreted with a higher complexity of ingredients (Spence and Wang, 2018). However, chemosensory perception is relative to exposed stimuli and simple tastes can be associated with complex chemistry when intense tastes mask weaker tastes, or when tastants are blended (Breslin and Beauchamp, 1997; Green et al., 2010). For example, starchy flavours or sweet tastes can be sensed when bitter and astringent antifeedant compounds are present below a certain threshold while salts enhance overall flavour by suppressing the perception of bitter tastants (Breslin and Beauchamp, 1997; Johns, 1990). On the other hand, combinations of different tastants or olfactory stimuli do not necessarily result in increased perceived complexity (Spence and Wang, 2018; Weiss et al., 2012). The relationship between intense chemosensation and versatility (**Figure 2**) is consistent with a perceived causal link between strong sensations and strong effects that is probably innate (Ganchrow et al., 1983; Glendinning, 1994). We also detected nuances in significance, and complete absence of significance across the relationships between individual therapeutic uses and complexity/intensity magnitudes for which we lack, however, more specific explanations (**Figure 2–Figure supplement 1**).

Low therapeutic versatility of sour tasting drugs (12 negative associations) may best be understood by considering the uses that this taste was negatively associated with in our

PGLMMs (**Figure 3**). For example, the significant association between sour and treatment of coughs (p_x = 0.038) and other respiratory problems (p_x = 0.042; **Figure 3; Supplementary files 5 and 6**) might be related to coughing triggered by acid signalling in in the airways (Kollarik et al., 2007). Moreover, acidic solutions and tissue acidosis are associated with inflammation and nociception while acid reflux is a common cause of chronic cough probably triggered by an oesophageal-bronchial reflex (Irwin, 2006). The negative associations of sour but also salty drugs with pain management (p_x = 0.021 and 0.022, respectively; **Figure 3; Supplementary files 5 and 6**), are probably related to the avoidance of nociception known by personal experience to result from the contact between acidic or salty solutions and skin or mucous membrane lesions.

The therapeutic versatility of drugs perceived as sweet (13 positive associations) and starchy (12 positive associations) (**Figure 3; Supplementary files 5 and 6**) is influenced by the many staples and edible fruits that are also used for medicine (e.g., protein-rich Fabaceae seeds were often perceived as having starchy tastes). The daily use of food items, generally with a low toxicity, has allowed for a more detailed comprehension of their postprandial effects, which arguably has led to a diversification of uses. The 96 botanical drugs specifically mentioned also for food (though, there are more than 150 edible drugs in our dataset; **Supplementary file 1**) show positive associations with starchy (p_x = 0.005), nutty (p_x = 0.002) and salty (p_x = 0.001) and negative associations with bitter (p_x = 0.007), woody (p_x = 0.001) and stinging (p_x = 0.033) chemosensory qualities.

Sweet sensations are known to induce analgesia (Kakeda et al., 2010) reflected here by a positive association of sweet tasting drugs with the treatment of pain (p_x = 0.032). Both starchy (p_x = 0.001) and salty (p_x = 0.002) are associated with the treatment of diarrhoea and dysentery. Today, mixtures of glucose, starch and electrolytes are used to treat secretolytic and inflammatory diarrhoea caused by bacterial enterotoxins (Thiagarajah et al., 2015; Binder

et al., 2014). These oral rehydration solutions exploit sodium/glucose co-transport by sodium/glucose co-transporter 1 in the small intestine and sodium absorption through sodium–hydrogen antiporter 2 stimulated by short chain fatty acids synthesized from starch by bacteria in the colon (Thiagarajah et al., 2015; Binder et al., 2014). Drugs perceived as starchy are also positively associated with the treatment of topical ulcers ($p_x = 0.001$), skin infections ($p_x = 0.025$), other skin conditions ($p_x = 0.035$) and the topical treatment of venomous and non-venomous animal bites ($p_x = 0.001$) where plasters with lenitive properties might bring benefit. Moreover, fresh Fabaceae seeds contain protease inhibitors (Birk, 1996; Wink and Waterman, 1999) such as trypsin and chymotrypsin inhibitors, which have the potential to inhibit bacterial proteases and control bacterial virulence during cutaneous infections (Frees et al., 2013; Culp and Wright, 2017).

Bitter was the most frequently reported chemosensory quality and showed nine significant associations with therapeutic use – including the negative association with foods (**Figure 3**). Though many bitter compounds are toxic, not all bitter plant metabolites are (Glendinning, 1994; Drewnoswski and Gomez-Carneros, 2000; e.g., iridoids, flavonoids, glucosinolates, bitter sugars). In part, this may be the outcome of an arms race between plant defence and herbivorous mammals' bitter taste receptor sensitivities, resulting in the synthesis of metabolites capable of repelling herbivores and confounding the perception of potential nutrients by mimicking tastes of toxins. Here, poisons showed no association with bitter but positive associations with aromatic ($p_x = 0.041$), sweet ($p_x = 0.022$) and soapy ($p_x = 0.025$) as well as a negative association with salty ($p_x = 0.046$) qualities.

Anti-inflammatory pharmacology of several bitter tasting compounds explains the positive associations with treatments of sciatica ($p_x = <0.001$; **Figure 3**). Bitter tasting drugs to treat sciatica derive from several disparate lineages containing a range of different anti-inflammatory compound classes such as iridoids (Viljoen et al., 2012; *Ajuga*, *Centaurium*),

sesquiterpene lactones (Coricello, 2020; *Artemisia*, *Inula*), triterpene saponines (Gepdiremen et al., 2006; Wang et al., 2014; *Citrullus*, *Ecballium*, *Leontice*), and cumarins (Kirsch et al., 2016; *Opopanax*, *Ruta*) (**Supplementary files 1 and 2**).

Generally, overarching explanations for versatility based on chemosensory perception are not feasible. However, we hypothesize that many of the associations we found (**Figure 3; Supplementary files 5 and 6**) are grounded in observed physiological effects mediated by chemesthesis and taste receptor pharmacology (Chandrashekar et al., 2006; Palmer and Servant, 2022). Cumulative evidence suggests that together with transient receptor potential channels (TRPs), extraoral taste receptors and ectopic olfactory receptors form a chemosensory network involved in homeostasis, disease response and off-target drug effects (Foster et al., 2014; An and Liggett, 2018; Kang and Koo, 2012; Hauser et al., 2017; Clark et al., 2012). Bitter taste receptors, for instance, are located also in human airways where their activation mediates bronchodilation and the movement of motile cilia which leads to improved respiration and evacuation of mucus (Shah et al., 2009; Deshpande et al., 2010). Indeed, bitter showed positive associations with the treatment of breathing difficulties (p_x = 0.027) and other respiratory problems (p_x = 0.004). We find that drugs used to treat pain, including pain associated with breastfeeding (breast inflammation and lactation), are significantly more likely to have fresh and cooling qualities (p_x = 0.01 and 0.037, respectively). This is likely owing to interactions with TRP channels (McKemy et al., 2002; Behrendt et al., 2004; Proudfoot et al., 2006; Memon et al., 2019). Specifically, the TRPM8 channel mediates cold stimuli and is known to be activated by cooling essential oil constituents producing analgesic effects (McKemy et al., 2002; Behrendt et al., 2004; Proudfoot et al., 2006). Cooling menthol and eucalyptol have been shown to act as counterirritants inhibiting respiratory irritation caused by smoke constituents (Willis et al., 2011) explaining the positive association between drugs used to treat breathing difficulties

with fresh and cooling flavours (p_x = 0.04). The strong positive association of burning and hot drugs with oral applications for treating musculoskeletal problems (p_x = 0.004) might be related to analgesic properties mediated by desensitizing effects upon TRP channel interaction (Marwaha et al., 2016; Aroke et al., 2020). Burning and hot drugs are also positively associated with vascular problems (p_x = 0.042) including varices and haemorrhoids and can be explained with vasorelaxant effects transmitted by TRP channels on the endothelial cells (Montell, 2005; Pires and Earley, 2017). TRPV channels are also involved in kidney and urinary bladder functioning (Montell, 2005) and TRPV1-knockout mice urinate more frequently without voiding their bladder (Birder et al., 2002). Interactions with TRPV1 and other TRPV receptors might therefore explain the use of hot botanical drugs to treat other urinary problems including urinary retention, incontinence, kidney and bladder problems (p_x = 0.047).

The concepts of humoral medicine may have derived from the observation that the appearance and consistency of bodily fluids during disease change and that they can be modified. The positive association of bitter taste with humoral management (p_x = 0.004) as well as with liver problems and jaundice (p_x = 0.002) is explained by uses intended to purge and resolve bitter bile and seems to include what we call choleretics and cholekinetics today, such as the roots of the great yellow gentian (*Gentiana lutea*) or the herb of the common vervain (*Verbena officinalis*). Astringency and woody qualities showed positive associations with the treatment of diarrhoea and dysentery (p_x = 0.029 and p_x = 0.019) where there is a need for controlling the flow of fluids and for drying them up. Similarly woody, often correlating with astringency (Scalbert et al., 1989) was also positively associated with the staunching of vaginal discharge (p_x = <0.001). Curiously, astringency showed positive associations with external applications for musculoskeletal conditions (p_x = 0.001) where drying internal bleeds and solidifying tissues and bones are needed. Negative associations of

astringency emerged with conditions where the flux of humours, perspiration and the evacuation of liquids and mucus are treatment strategies, such as in fever ($p_x = 0.045$), humoral management ($p_x = 0.02$), urinary calculus ($p_x = 0.02$), other urinary problems (retention, incontinence, kidney and bladder problems, $p_x = <0.001$) and cough ($p_x = 0.002$). More obviously, the intake of salt aggravates fluid retention and oedema, and this is likely the reason why remedies for dropsy and oedema (diuretics) are negatively associated with salty tastes ($p_x = 0.023$). Chemosensory qualities of botanical drugs and their physiological effects probably explain the persistence of humoral medicine until the 19th century.

Looking forwards, our study highlights the potential of chemosensory pharmacology in the development of herbal medicines. Botanical drugs with observed chemosensory profiles not aligned with those of their therapeutic use might represent drugs working beyond chemosensory pharmacology. Conversely, associations of chemosensory qualities with therapeutic uses of botanical drugs may certainly overlap with the presence of metabolites with specific therapy-relevant constituents acting beyond chemosensory pharmacology. This is, for instance, the case with opium (dried milk sap of *Papaver somniferum* L.) indicated for 'cough' and perceived as bitter (**Figure 3**; **Supplementary files 1 and 2**) but at the same time containing alkaloids with central cough suppressant properties (Dewick, 2002). Besides the associations discussed, other therapeutically relevant chemosensory receptor functions might be involved in the associations currently lacking explanations. While we are aware that the limitation of this study is the impossibility to address all associations found and the dependence on published pharmacological data for the explanatory part, our approach demonstrates the power of phylogenetic methods applied to human behaviour and assessment of plant properties. We show that chemosensory perception connects ancient therapeutic knowledge with modern science, even though aetiologies were fundamentally different in

Graeco-Roman times. Our study offers a blueprint for macroscale re-evaluation of pre-scientific knowledge and points towards a central role for taste and flavour in medicine.

Methods

Botanical fieldwork

A total of 700 botanical drugs (ca. 70% of the botanical drugs described in *DMM*) associated with 407 species were collected from the wild, cultivated in home gardens or purchased from commercial sources between 2014 and 2016. Plant collection included at least one voucher per species and one or more bulk samples of the therapeutic plant part (botanical drug). Latin binomials follow plantsoftheworldonline.org. Botanical vouchers were deposited at the herbarium of the University of Geneva (G) and the herbarium of the National and Kapodistrian University of Athens (ATHU). Bulk samples for sensory analysis were dried at 40–60° C and stored in plastic containers. Collection permits were obtained from the Greek Ministry of Environment and Energy (6Ω8K4653Π8-AK7).

Data extraction from *DMM*

Information about the therapeutic uses (use records) of botanical drugs were extracted from Matthioli's 1568 edition of Dioscorides' *De Materia Medica* (Matthioli, 1967-1970; Staub et al., 2016). Botanical drugs were arranged into 46 therapeutic uses defined by organ, therapeutic function, disease and symptom across 25 broader categories of use (**Figure 1; Supplementary files 1 and 4**). Each of the 700 botanical drugs was then assigned a binary variable defining whether it was recommended (1) or not (0) for each of the 46 therapeutic uses based on their descriptions in *DMM*. When the description in *DMM* permitted identification (Taxon ID; **Supplementary file 1**) only to genus level (due to ambiguities or the possibility that different closely related taxa were subsumed) we chose one species as the

representative for the whole genus (**Supplementary file 1**: 'Taxon panel'). Unidentified taxa or taxa identified only to the family level were not considered in this analysis. The category 'food' includes only those drugs where edibility was specifically mentioned in *DMM* and by far not all those that are used as food. As a measure of therapeutic versatility, we summed up the total number of broader categories of therapeutic use each botanical drug was recommended for.

Tasting panel

The chemosensory qualities of each of the 700 botanical drugs were assessed experimentally by trained human subjects using the sensory analysis technique Conventional Profiling (ISO 11035) performed in accordance with the Declaration of Helsinki (World Medical Association of Helsinki, 2013) and the ethics guidelines of the Institute of Food Science & Technology (Institute of Food Science and Technology, 2020). The study design was approved by the Ethics Committee of the University Hospital of Cagliari (NP/2016/4522). Informed consent was obtained from all research participants. We used 22 chemosensory descriptors to represent taste and flavour perception (**Figure 1; Supplementary files 2 and 3**). The evaluation took place at the Hospital of *San Giovanni di Dio* (Cagliari, Italy) during a period of five months in 2016. The panel consisted of eleven healthy Caucasian volunteers (six males and five females; age 30.7±7.4). Working language was Italian. Based on a random subset of 40 (out of 700) samples, four initial training sessions were held to establish a consensus regarding chemosensory terminology. Hedonic (e.g., "good" or "bad"), self-referential (e.g., "minty" for mint) and infrequent descriptors were excluded to reduce subjectivity and to increase discriminatory power of the analysis. Synonymous and closely related descriptors (e.g., "astringent" and "tannic") were pooled to reduce attribute redundancy.

Samples (0.1 to 2 g of dried drug pieces) were labelled randomly (using a random number generator) with three-digit codes, assigned randomly and double-blinded (in case of common drugs impossible) to individual panellists. Not all drugs were tasted by all panellists while random distribution permitted that individual panellists were challenged with repeated samples. Samples were presented in identical 125 ml plastic containers at room temperature. The relatively big range in quantity of dispensed samples owes to toxicological concerns and practical reasons but in any case, were tailored to permit the perception of their chemosensory qualities. Panellists were instructed to chew the amount of sample necessary for chemosensory perception, to annotate perceived qualities and intensities and to spit out residues of samples, and finally rinse their mouth with drinking water. The breaks between tasting different samples depended on the persistence of chemosensory perception. For each sensory trial a separate evaluation sheet was used. Quality intensities were evaluated on a 4-point ordinal scale: absent (0), weak (1), medium (2) and strong (3). Overall, 3973 individual sensory trials were conducted, with an average of 361±153 trials per panellist and 5.7±1.3 trials per botanical drug. On average each panellist tasted 17,2 drugs per hour using 10.5 sessions (18 sessions in total) lasting approximately two hours each. From the ordinal data, two additional metrics were calculated to represent chemosensory *complexity* (the total number of different chemosensory qualities a botanical drug was assigned to as non-zero by each panellist) and chemosensory *intensity* (the sum of all chemosensory scores assigned across all qualities by each panellist).

Phylogenetic tree

We used the species-level supertree of land plants to represent the relationships among the taxa extracted from *DMM* (Zanne et al., 2014). Some species were not found in the tree; in these cases, species were attached to the most recent common ancestor of the respective

genus or, if absent, the family. Branch lengths of added taxa were set to retain ultrametricity. Tree manipulations were made in R (R Core Team, 2016) using the packages APE and PHYTOOLS (Paradis et al., 2004; Revell, 2012). The trees are represented in **Figure 2** alongside the chemosensory intensity and complexity data.

Statistical procedure

In order, to determine whether chemosensation and therapeutic uses were linked, we used two sets of phylogenetic linear mixed models implemented in a Bayesian framework within the R package MCMCglmm (Hadfield, 2010). The first set of models considered therapeutic versatility (number of categories of therapeutic use) modelled as a zero-truncated poisson distributed response variable. We ran two models: (i) considering all 22 individual chemosensory qualities as ordinal-scale independent variables and (ii) considering chemosensory intensity and complexity as independent variables. Together, these models tell us whether any particular chemosensory quality as well as whether intense or complex chemosensation predict how often a drug is used for any therapeutic purpose. We then ran a second set of probit models which considered each individual therapeutic use as a binary response. That is, we ran 46 models examining the relationship between individual chemosensory qualities and therapeutic uses (one for each use, where all qualities are included as independent variables) and an additional 46 to test the relationship between each therapeutic use and chemosensory intensity and complexity.

The significance of all parameters is assessed using the proportion of the posterior distribution of parameter estimates that cross zero (p_x). If a parameter has a substantial effect on a model, we expect the distribution of parameter estimates to be shifted away from zero (i.e., $p_x < 0.5$). All models were run for a total of 500,000 iterations after burn-in, sampling every 5,000.

Phylogenetic signal was calculated using heritability (h^2) which has an identical interpretation to Pagel's lambda. All models showed high heritability values ($h^2 > 0.9$) demonstrating the importance of species' shared ancestry (h^2 ranges between 0 and 1, and values close to 1 indicate very strong phylogenetic signal). In all models we included plant part, panellist ID, and the phylogenetic matrix as random effects. The inclusion of plant part and the phylogenetic matrix allowed for the fact that in some cases, multiple drugs were extracted from different parts of the same plant (e.g., *Vitis vinifera* L., fruit; leaf, herb, seeds) whilst still accounting for the overall underlying evolutionary relationships. The inclusion of panellist ID removed the effect of any biased perception by single panellists across drugs as well as any differences among panellists for an individual drug. We also included the number of days between sample collection and when each sample was tasted, in order, to account for any degradation of samples over time that may have affected chemosensory perception. For all fixed factors in all models, we used largely uninformative priors (implementing a normal distribution with a mean of 0 and a variance of 1e10). Residual variance was estimated using an inverse gamma prior (V = 1, nu = 0.002). We used parameter-expanded priors (roughly uniform standard deviations) for all random effects including phylogenetic variance (Hadfield and Nakagawa, 2010).

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Author Contributions:

Marco Leonti, Conceptualization; Methodology, Formal analysis; Investigation; Resources; Data curation; Writing – original draft preparation; Writing – review & editing; Supervision; Project administration; Funding acquisition; Joanna Baker, Methodology; Software; Validation; Formal analysis; Investigation; Writing – original draft preparation; Writing – review & editing; Visualisation; Peter Staub, Conceptualization; Methodology; Investigation; Data curation; Laura Casu, Methodology; Resources; Data curation; Project administration; Julie Hawkins, Investigation; Writing – original draft preparation; Writing – review & editing; Supervision.

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References

An SS, Liggett SB. Taste and smell GPCRs in the lung: Evidence for a previously unrecognized widespread chemosensory system. Cell Signal. 2018 Jan;41:82-88. doi: 10.1016/j.cellsig.2017.02.002.

Aroke EN, Powell-Roach KL, Jaime-Lara RB, Tesfaye M, Roy A, Jackson P, Joseph PV. Taste the Pain: The Role of TRP Channels in Pain and Taste Perception. Int J Mol Sci. 2020 Aug 18;21(16):5929. doi: 10.3390/ijms21165929.

Behrendt HJ, Germann T, Gillen C, Hatt H, Jostock R. Characterization of the mouse cold-menthol receptor TRPM8 and vanilloid receptor type-1 VR1 using a fluorometric imaging

plate reader (FLIPR) assay. Br J Pharmacol. 2004 Feb;141(4):737-45. doi: 10.1038/sj.bjp.0705652.

Binder HJ, Brown I, Ramakrishna BS, Young GP. Oral rehydration therapy in the second decade of the twenty-first century. Curr Gastroenterol Rep. 2014 Mar;16(3):376. doi: 10.1007/s11894-014-0376-2.

Birder LA, Nakamura Y, Kiss S, Nealen ML, Barrick S, Kanai AJ, Wang E, Ruiz G, De Groat WC, Apodaca G, Watkins S, Caterina MJ. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci. 2002 Sep;5(9):856-60. doi: 10.1038/nn902.

Birk Y. Protein proteinase inhibitors in legume seeds--overview. Arch Latinoam Nutr. 1996 Dec;44(4 Suppl 1):26S-30S.

Breslin, P.A., 2013. An evolutionary perspective on food and human taste. Curr Biol. 23, R409–418. doi: 10.1016/j.cub.2013.04.010.

Breslin PA, Beauchamp GK. Salt enhances flavour by suppressing bitterness. Nature. 1997 Jun 5;387(6633):563. doi: 10.1038/42388.

Casagrande, D. G. Human Taste and Cognition in Tzeltal Maya Medicinal Plant Use. J. Ecol. Anthropol. 4, 57–68 (2000). https://digitalcommons.usf.edu/jea/vol4/iss1/3

Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. Nature. 2006 Nov 16;444(7117):288-94. doi: 10.1038/nature05401.

Coricello A, Adams JD, Lien EJ, Nguyen C, Perri F, Williams TJ, Aiello F. A Walk in Nature: Sesquiterpene Lactones as Multi-Target Agents Involved in Inflammatory Pathways. Curr Med Chem. 2020;27(9):1501-1514. doi: 10.2174/0929867325666180719111123.

Clark AA, Liggett SB, Munger SD. Extraoral bitter taste receptors as mediators of off-target drug effects. FASEB J. 2012 Dec;26(12):4827-31. doi: 10.1096/fj.12-215087.

Culp E, Wright GD. Bacterial proteases, untapped antimicrobial drug targets. J Antibiot (Tokyo). 2017 Apr;70(4):366-377. doi: 10.1038/ja.2016.138.

Deshpande DA, Wang WC, McIlmoyle EL, Robinett KS, Schillinger RM, An SS, Sham JS, Liggett SB. Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. Nat Med. 2010 Nov;16(11):1299-304. doi: 10.1038/nm.2237.

Dewick, P., 2002. Medicinal Natural Products. A Biosynthetic Approach. Wiley, Chichester.

Dragos D, Gilca M. Taste of phytocompounds: A better predictor for ethnopharmacological activities of medicinal plants than the phytochemical class? J Ethnopharmacol. 2018 Jun 28;220:129-146. doi: 10.1016/j.jep.2018.03.034.

Drewnowski A, Gomez-Carneros C. Bitter taste, phytonutrients, and the consumer: a review. Am J Clin Nutr. 2000 Dec;72(6):1424-35. doi: 10.1093/ajcn/72.6.1424.

Einarson, B. & Link, G. K. K. 1990. Theophrastus. De Causis Plantarum Books V-VI (Harvard Univ. Press, Cambridge, 1990).

Foster SR, Roura E, Thomas WG. Extrasensory perception: odorant and taste receptors beyond the nose and mouth. Pharmacol Ther. 2014 Apr;142(1):41-61. doi: 10.1016/j.pharmthera.2013.11.004.

Frees, D., Brøndsted, L. & Ingmer, H. 2013. Bacterial proteases and virulence. Subcell. Biochem. 66, 161–192 (2013). doi: 10.1007/978-94-007-5940-4_7.

Ganchrow, J. R., Steiner, J. E. & Daher, M. Neonatal facial expressions in response to different qualities and intensities of gustatory stimuli. Infant Behav. Dev. 6, 189–200 (1983). https://doi.org/10.1016/S0163-6383(83)90301-6.

Gepdiremen A, Mshvildadze V, Bakuridze K, Elias R. Effects of Leontice smirnowii tuber monodesmosides and crude extract in carrageenan- and histamine-induced acute inflammation model of rats. Phytomedicine. 2006 Nov;13(9-10):728-31. doi: 10.1016/j.phymed.2005.09.011.

Gertsch J. Botanical drugs, synergy, and network pharmacology: forth and back to intelligent mixtures. Planta Med. 2011 Jul;77(11):1086-98. doi: 10.1055/s-0030-1270904.

Glendinning JI. Is the bitter rejection response always adaptive? Physiol Behav. 1994 Dec;56(6):1217-27. doi: 10.1016/0031-9384(94)90369-7.

Glendinning, J.I., 2022. What Does the Taste System Tell Us About the Nutritional Composition and Toxicity of Foods? Pp. 321-351, In: Palmer, K., Servant, (eds.) The Pharmacology of Taste. Springer International Publishing.

Green BG, Lim J, Osterhoff F, Blacher K, Nachtigal D. Taste mixture interactions: suppression, additivity, and the predominance of sweetness. Physiol Behav. 2010 Dec 2;101(5):731-7. doi: 10.1016/j.physbeh.2010.08.013.

Hadfield, J. D. MCMC methods for multi-response generalized linear mixed models: The MCMCglmm R package. J. Stat. Softw. 33, 1–22 (2010). 10.18637/jss.v033.i02.

Hadfield JD, Nakagawa S. General quantitative genetic methods for comparative biology: phylogenies, taxonomies and multi-trait models for continuous and categorical characters. J Evol Biol. 2010 Mar;23(3):494-508. doi: 10.1111/j.1420-9101.2009.01915.x.

Hauser AS, Attwood MM, Rask-Andersen M, Schiöth HB, Gloriam DE. Trends in GPCR drug discovery: new agents, targets and indications. Nat Rev Drug Discov. 2017 Dec;16(12):829-842. doi: 10.1038/nrd.2017.178.

Institute of Food Science and Technology. Guidelines for Ethical and Professional Practices for the Sensory Analysis of Foods. http://www.ifst.org/knowledge-centre-other-knowledge/ifst-guidelines-ethical-and-professional-practices-sensory (2020).

Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):80S-94S. doi: 10.1378/chest.129.1_suppl.80S.

ISO 11035 International Standard. Sensory analysis - Identification and selection of descriptors for establishing a sensory profile by a multidimensional approach (International Standard Organisation, Geneva). https://www.iso.org/standard/19015.html (1994).

Johns, T. With bitter herbs they shall eat it: Chemical ecology and the origins of human diet and medicine (Univ. of Arizona Press, Tucson, 1990).

Jones, W. H. S. 1959. Hippocrates, Volume IV, Heracleitus on the Universe. With an English translation by W. H. S Jones (H. Heinemann, London, Harward Univ. Press, Cambridge Massachusetts, 1959).

Jouanna, J. & Allies, N. Greek Medicine from Hippocrates to Galen: Selected Papers. (ed. Van der Eijk, P., Brill, Leiden 2012).

Kakeda T, Ogino Y, Moriya F, Saito S. Sweet taste-induced analgesia: an fMRI study. Neuroreport. 2010 Apr 21;21(6):427-31. doi: 10.1097/WNR.0b013e3283383df5.

Kang N, Koo J. Olfactory receptors in non-chemosensory tissues. BMB Rep. 2012 Nov;45(11):612-22. doi: 10.5483/bmbrep.2012.45.11.232.

King, H. in The Body in Balance. Humoral Medicines in Practice (eds. Horden, P. & Hsu, E.) 25–52 (Berghahn, New York, 2013).

Kirsch G, Abdelwahab AB, Chaimbault P. Natural and Synthetic Coumarins with Effects on Inflammation. Molecules. 2016 Oct 2;21(10):1322. doi: 10.3390/molecules21101322.

Kollarik M, Ru F, Undem BJ. Acid-sensitive vagal sensory pathways and cough. Pulm Pharmacol Ther. 2007;20(4):402-11. doi: 10.1016/j.pupt.2006.11.010.

Leonti M, Sticher O, Heinrich M. Medicinal plants of the Popoluca, México: organoleptic properties as indigenous selection criteria. J Ethnopharmacol. 2002 Aug;81(3):307-15. doi: 10.1016/s0378-8741(02)00078-8.

Lindemann, B., 2001. Receptors and transduction in taste. Nature 413, 219–225.

Marwaha L, Bansal Y, Singh R, Saroj P, Bhandari R, Kuhad A. TRP channels: potential drug target for neuropathic pain. Inflammopharmacology. 2016 Dec;24(6):305-317. doi: 10.1007/s10787-016-0288-x.

Matthioli, P. A. I Discorsi di M. Pietro Andrea Matthioli. Sanese, Medico Cesareo, et del Serenissimo Principe Ferdinando Archiduca d'Austria & c. Nelli Sei Libri di Pedacio Dioscoride Anazarbeo della Materia Medicale (Stabilimento Tipografico Julia, Rome, 1967–1970).

McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature. 2002 Mar 7;416(6876):52-8. doi: 10.1038/nature719.

Memon T, Yarishkin O, Reilly CA, Križaj D, Olivera BM, Teichert RW. trans-Anethole of Fennel Oil is a Selective and Nonelectrophilic Agonist of the TRPA1 Ion Channel. Mol Pharmacol. 2019 Apr;95(4):433-441. doi: 10.1124/mol.118.114561.

Mennella JA, Spector AC, Reed DR, Coldwell SE. The bad taste of medicines: overview of basic research on bitter taste. Clin Ther. 2013 Aug;35(8):1225-46. doi: 10.1016/j.clinthera.2013.06.007.

Montell C. The TRP superfamily of cation channels. Sci STKE. 2005 Feb 22;2005(272):re3. doi: 10.1126/stke.2722005re3.

Nissim, I., Dagan-Wiener, A., Niv, M.Y., 2017. The taste of toxicity: A quantitative analysis of bitter and toxic molecules. IUBMB Life. 69, 938–946. doi: 10.1002/iub.1694.

Palmer, K. & Servant, G. The Pharmacology of Taste (Springer International Publishing, 2022).

Paradis E, Claude J, Strimmer K. APE: Analyses of Phylogenetics and Evolution in R language. Bioinformatics. 2004 Jan 22;20(2):289-90. doi: 10.1093/bioinformatics/btg412.

Pires PW, Earley S. Redox regulation of transient receptor potential channels in the endothelium. Microcirculation. 2017 Apr;24(3):10.1111/micc.12329. doi: 10.1111/micc.12329.

Proudfoot CJ, Garry EM, Cottrell DF, Rosie R, Anderson H, Robertson DC, Fleetwood-Walker SM, Mitchell R. Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. Curr Biol. 2006 Aug 22;16(16):1591-605. doi: 10.1016/j.cub.2006.07.061.

R Core Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ (2016).

Revell, L. J. phytools: An R package for phylogenetic comparative biology (and other things). Methods Ecol. Evol. 3, 217–223 (2012). https://doi.org/10.1111/j.2041-210X.2011.00169.x

Riddle, J. M. Dioscorides on Pharmacy and Medicine (Univ. of Texas Press, Austin, 1985).

Rozin, P., Todd, P.M., 2016. The Evolutionary Psychology of Food Intake and Choice. Pp. 183-205 in Buss, D.M., (Edtr.). Handbook of Evolutionary Psychology, Second Edition, edited by David M. Buss. John Wiley & Sons, Inc.

Scalbert, A., Bernard, M. & Janin, G. Tannins in wood: comparison of different estimation methods. J. Agric. Food Chem. 37, 1324–1329 (1989). https://doi.org/10.1021/jf00089a026.

Shepard, G. A sensory ecology of medicinal plant therapy in two Amazonian societies. Am. Anthropol. 106, 252–266 (2004). https://www.jstor.org/stable/3566962

Shah, A. S., Ben-Shahar, Y., Moninger, T. O., Kline, J. N. & Welsh, M. J. Motile cilia of human airway epithelia are chemosensory. Science 325, 1131–1134 (2009). Shah AS, Ben-Shahar Y, Moninger TO, Kline JN, Welsh MJ. Motile cilia of human airway epithelia are chemosensory. Science. 2009 Aug 28;325(5944):1131-4. doi: 10.1126/science.1173869.

Shou-zhong, Y. The Divine Farmer's Materia Medica: A Translation of the Shen Nong Ben Cao Jing (Blue Poppy Press, Boulder, 1998).

Spence C, Wang QJ. On the Meaning(s) of Perceived Complexity in the Chemical Senses. Chem Senses. 2018 Aug 24;43(7):451-461. doi: 10.1093/chemse/bjy047.

Staub PO, Casu L, Leonti M. Back to the roots: A quantitative survey of herbal drugs in Dioscorides' De Materia Medica (ex Matthioli, 1568). Phytomedicine. 2016 Sep 15;23(10):1043-52. doi: 10.1016/j.phymed.2016.06.016.

Thiagarajah JR, Donowitz M, Verkman AS. Secretory diarrhoea: mechanisms and emerging therapies. Nat Rev Gastroenterol Hepatol. 2015 Aug;12(8):446-57. doi: 10.1038/nrgastro.2015.111.

Touwaide, A. in A Cultural History of Plants. Plants and Medicine (ed. Giesecke A.) 109–130 (Bloomsbury Academic, London, 2022).

Viljoen A, Mncwangi N, Vermaak I. Anti-inflammatory iridoids of botanical origin. Curr Med Chem. 2012;19(14):2104-27. doi: 10.2174/092986712800229005.

Wagner, H., Vollmar, A. & Bechthold, A. Pharmazeutische Biologie 2 (Wissenschaftliche Verlagsgesellschaft, mbH, Stuttgart, 2007).

Wang Y, Zhao GX, Xu LH, Liu KP, Pan H, He J, Cai JY, Ouyang DY, He XH. Cucurbitacin IIb exhibits anti-inflammatory activity through modulating multiple cellular behaviors of mouse lymphocytes. PLoS One. 2014 Feb 25;9(2):e89751. doi: 10.1371/journal.pone.0089751.

Weiss T, Snitz K, Yablonka A, Khan RM, Gafsou D, Schneidman E, Sobel N. Perceptual convergence of multi-component mixtures in olfaction implies an olfactory white. Proc Natl Acad Sci U S A. 2012 Dec 4;109(49):19959-64. doi: 10.1073/pnas.1208110109.

Willis DN, Liu B, Ha MA, Jordt SE, Morris JB. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. FASEB J. 2011 Dec;25(12):4434-44. doi: 10.1096/fj.11-188383.

Wink, M. & Waterman, P. in: Biochemistry of Plant Secondary Metabolism (ed. Wink, M.) 300–341 (John Wiley and Sons Ltd, Oxford, 1999).

World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4. doi: 10.1001/jama.2013.281053.

Zanne AE, Tank DC, Cornwell WK, Eastman JM, Smith SA, FitzJohn RG, McGlinn DJ, O'Meara BC, Moles AT, Reich PB, Royer DL, Soltis DE, Stevens PF, Westoby M, Wright IJ, Aarssen L, Bertin RI, Calaminus A, Govaerts R, Hemmings F, Leishman MR, Oleksyn J, Soltis PS, Swenson NG, Warman L, Beaulieu JM. Three keys to the radiation of angiosperms into freezing environments. Nature. 2014 Feb 6;506(7486):89-92. doi: 10.1038/nature12872.

Figure 1. The 22 chemosensory qualities and 46 therapeutic uses studied here. Each chemosensory quality and use is represented by an icon that is used throughout the manuscript. Therapeutic uses that share an icon are considered to represent the same category of use (25 in total); these are linked by grey bars.

Figure 2. Drugs eliciting strong overall chemosensory perception (intense drugs) associated with relatively few perceived unique tastes (less complex) predict the number of categories of therapeutic use (therapeutic versatility). We show the distribution of intensity (**A**) and complexity (**B**) at the tips of the phylogenetic tree. As some species are represented by multiple parts, an average is shown here for representative purposes; each plant part is considered separately in the analysis. We plot the mean regression line as estimated from the parameter estimates of our Bayesian phylogenetic regression analyses (dark line) along with 100 random samples of the posterior distribution (faded lines). For graphical representation, the slopes are estimated holding other effects at their mean. We do this for both the significant positive association between intensity and therapeutic versatility (**C**, $p_x = <0.001$)

and the significant negative association between chemosensory complexity and therapeutic complexity (**D**, $p_x = 0.008$).

The online version of this article includes the following figure supplement for **Figure 2**.

Figure supplement 1. The relationship between individual therapeutic uses and chemosensory intensity/complexity.

Figure 2–figure supplement 1. The relationship between individual therapeutic uses and chemosensory intensity/complexity.

Chemosensory intensity and complexity were significantly associated with seventeen uses. No therapeutic use was predicted by weaker qualities. An arrow is shown indicating the direction of any significant association ($p_x < 0.05$) with either chemosensory intensity (left) or chemosensory complexity (right). An arrow points upward if a drug is more likely to be used for a given purpose with increasing chemosensory intensity or complexity. Arrows are shaded by the strength of the relationship (magnitude of estimated parameter, see scale). For seven individual uses more intense and less complex chemosensation increased the probability of a drug being used i.e., there was a preference for stronger and simpler qualities. Nine uses had a significant positive association with chemosensory intensity and were predicted by stronger qualities alone. A single use (various urinary problems) was uniquely significantly associated with increased chemosensory complexity. No therapeutic use was predicted by weaker qualities.

Figure 3. The magnitude of effect for 22 different specific chemosensory qualities across 46 different therapeutic uses. (**A**) A heat map showing the strength of the association between

specific qualities (columns) and therapeutic uses (rows). Where we find a significant association between the strength of chemosensory quality and whether a drug is used for a particular therapeutic purpose in our phylogenetic binary (probit) response model, the corresponding cell is coloured according to its estimated parameter value; see colour scale in panel (**B**). All other variables are zeroed and coloured white for visualization. (**B**) An overall 'magnitude of effect' is calculated for each chemosensory quality by summing the significant betas ($p_x < 0.05$, i.e., those displayed in the heat-map above) across all different uses and plotted as bars coloured by their magnitude; see colour scale alongside axis. The sum of all betas regardless of significance are shown as grey bars. Note that the large parameter estimate for "smoky" is owing to the fact that no botanical drug with any smoky quality (scored by any participant) is ever used for androgynous therapeutic purposes and thus is poorly estimated in that model (**Supplementary files 1,2,5 and 6**).

Supplementary files

Supplementary file 1. Sampled botanical drugs and their uses *ex* Matthioli (1568).

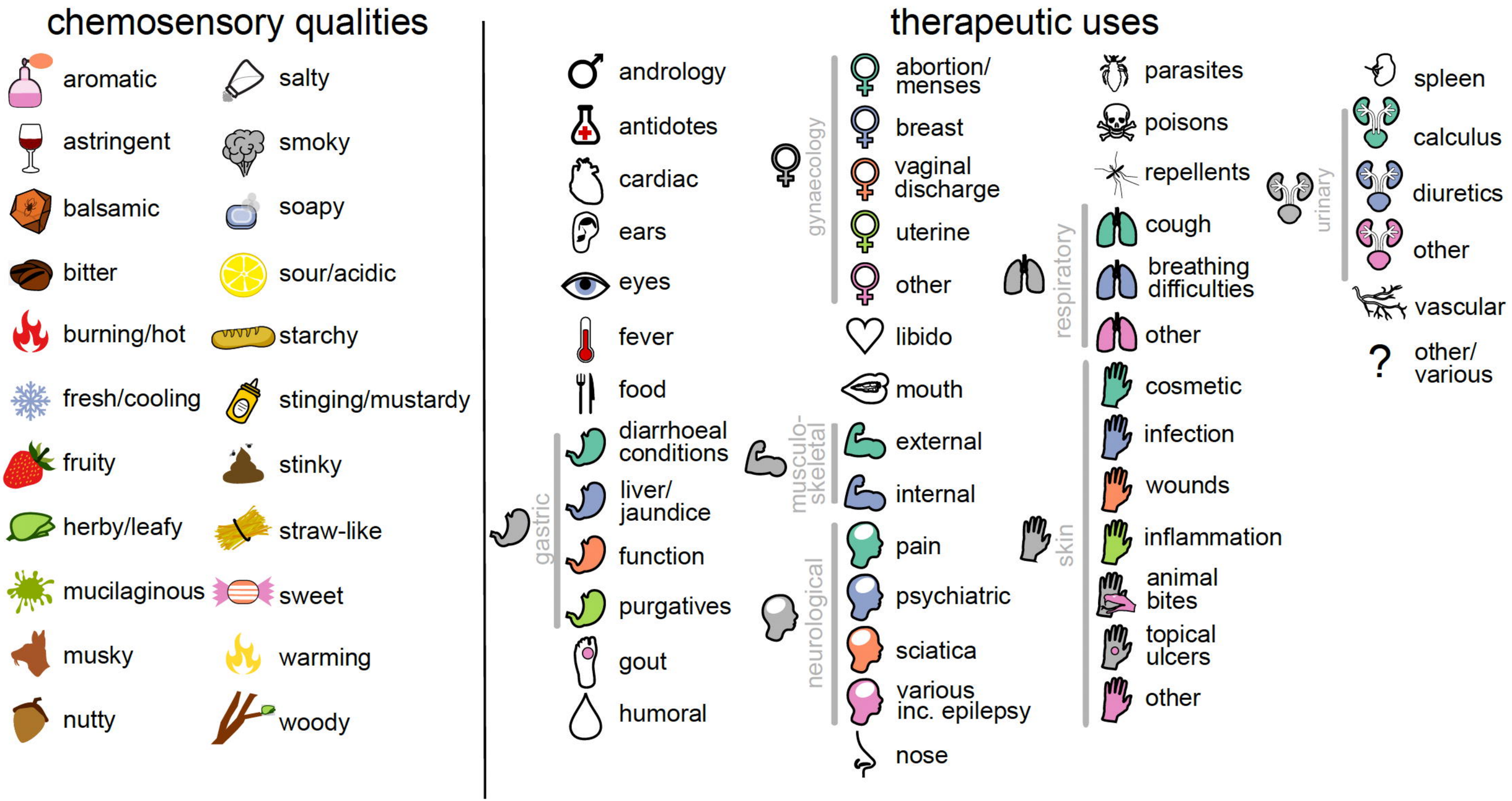
Supplementary file 2. Sampled botanical drugs and their chemosensory qualities (panel data).

Supplementary file 3. Codes and the short descriptions of the 22 chemosensory descriptors to represent tastes and flavours.

Supplementary file 4. Codes and the short descriptions of the therapeutic uses.

Supplementary file 5. Heat map showing the strength of the association between chemosensory quality and therapeutic use.

Supplementary file 6. Significance of individual parameter estimates from the models of individual chemosensory quality against individual therapeutic use calculated as the proportion of the parameter estimate crossing zero, p_x.


chemosensory qualities
aromatic
astringent
balsamic
bitter
burning/hot
fresh/cooling
fruity
herby/leafy
mucilaginous
musky
nutty
salty
smoky
soapy
sour/acidic
starchy
stinging/mustardy
stinky
straw-like
sweet
warming
woody
therapeutic uses
andrology
antidotes
cardiac
ears
eyes
fever
food
gastric
diarrhoeal conditions
liver/ jaundice
function
purgatives
gout
humoral
gynaecology
abortion/ menses
breast
vaginal discharge
uterine
other
libido
mouth
musculo-skeletal
external
internal
neurological
pain
psychiatric
sciatica
various inc. epilepsy
nose
respiratory
cough
breathing difficulties
other
skin
cosmetic
infection
wounds
inflammation
animal bites
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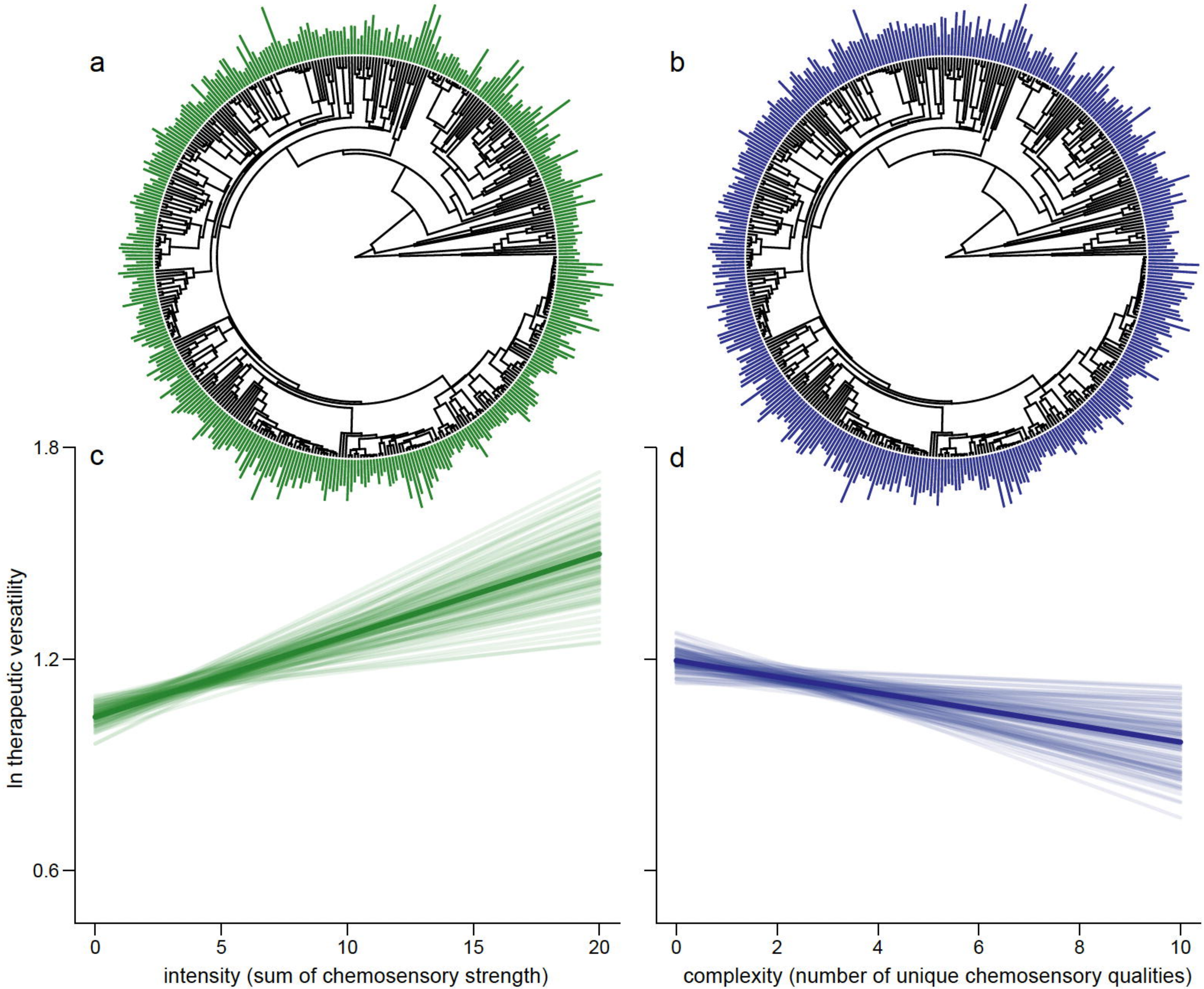
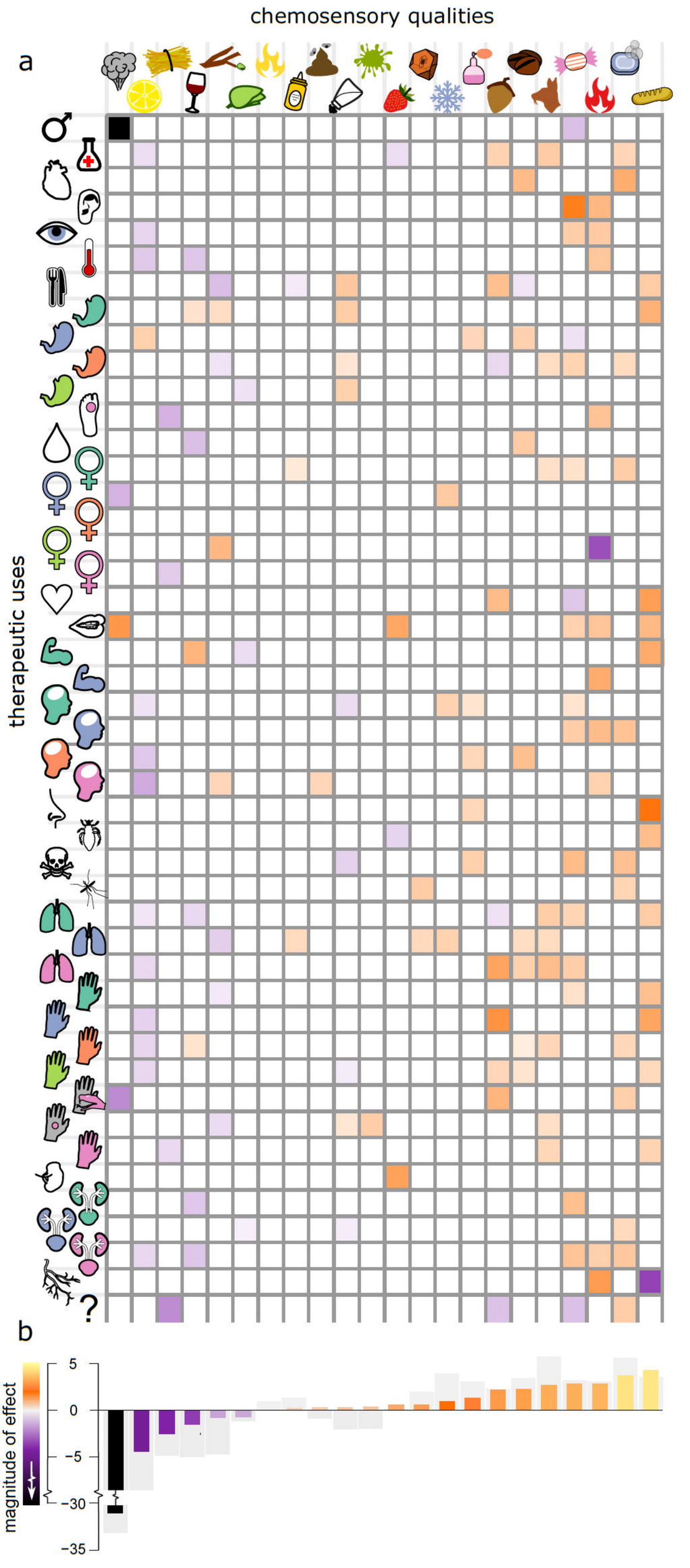
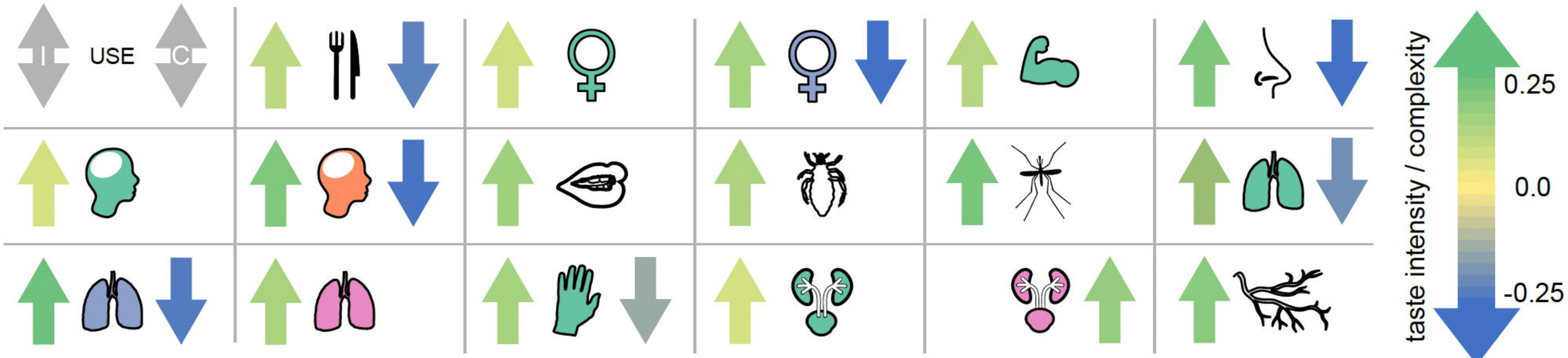
diuretics
other
vascular
other/ various


a
b
c
d
1.8
1.2
0.6
ln therapeutic versatility
0
5
10
15
20
intensity (sum of chemosensory strength)
0
2
4
6
8
10
complexity (number of unique chemosensory qualities)


chemosensory qualities
a
therapeutic uses
?
b
magnitude of effect
5
0
−5
−30
−35


I
USE
C
taste intensity / complexity
0.25
0.0
-0.25