8
Data-Driven Analysis Suggests Broad-Spectrum Benefits of Culinary Spices and Herbs

8.1 INTRODUCTION

The previous Chapter showed that systematic mining of biomedical literature for disease associations of culinary spices herbs reveal a vast number of disease associations, both positive and negative. We also linked spice phytochemicals to diseases with the help of available resources to explain the molecular basis of those positive and negative disease associations of culinary spices and herbs. In this Chapter, we perform data-driven analysis into the spice-disease associations. We find that spices show broad-spectrum benevolence across a range of disease categories in contrast to negative effects that are comparatively narrow-spectrum. We also implement a strategy for disease-specific culinary recommendations of spices based on their therapeutic tradeoff against adverse effects. Thus this Chapter throws light on the overall significance of culinary spices and herbs.

8.2 CATEGORY-LEVEL DISEASE ASSOCIATIONS OF CULINARY SPICES AND HERBS

As discussed earlier in Chapter 7, all disease terms were mapped to their corresponding MeSH headers. MeSH's descriptors, being organized from a more generic to a specific level. This provides a standard way of exploring the range of disease categories for which spices have positive and negative associations. To probe for the effects of spice/herb across a spectrum of disorders, we analyzed its associations with disease 'sub-categories' at the second level of the MeSH hierarchy (Figure 7.2). Analyzing associations at this level provides a balance between specificity and generality of disease terms. Among the disease sub-categories positively associated with spices, pathologic processes, signs and symptoms, metabolic diseases, diabetes mellitus, vascular diseases as well as central nervous system diseases were found to be dominant (Figure 8.1). Top disease categories that were negatively associated with spices included vascular diseases, skin diseases, hypersensitivity and respiratory hypersensitivity (Figure 8.2).

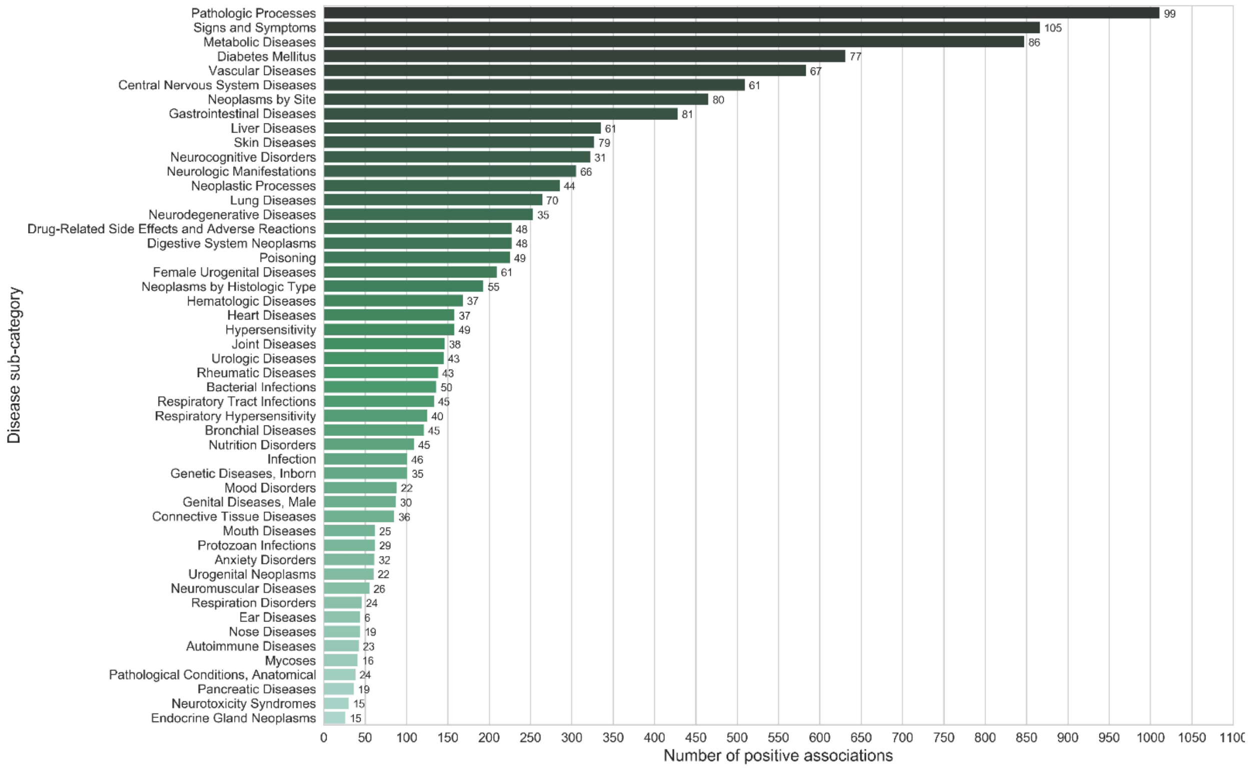

Figure 8.1: Disease categories (First level of MeSH hierarchy) ranked according to the number of positive associations with spices- Numbers shown against the bars indicate the 'number of spices' linked with each of the associations. The number of positive disease category associations for spices outnumbers those with negative associations, further confirming the benevolent health effects of spices.

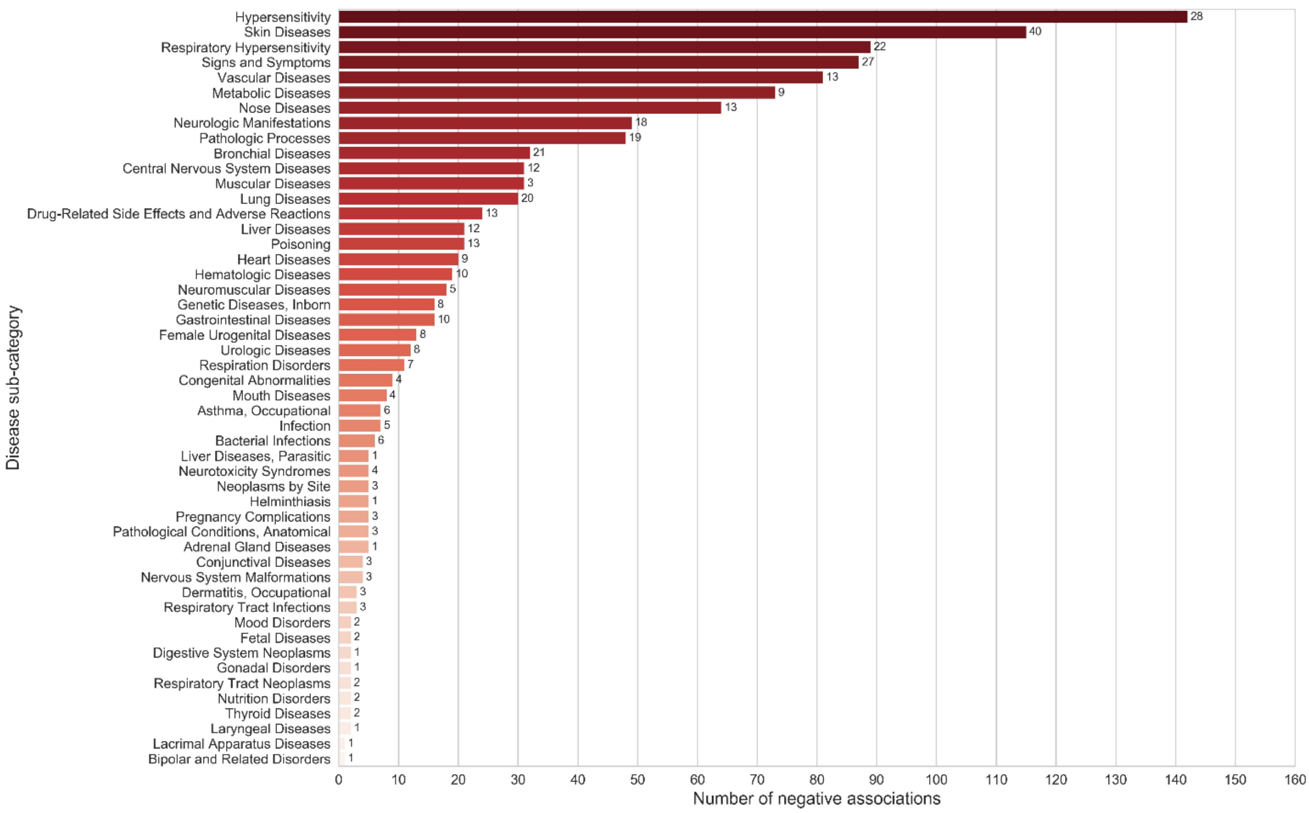

Figure 8.2: Disease categories (First level of MeSH hierarchy) ranked according to the number of negative associations with spices. Numbers shown against the bars indicate the 'number of spices' linked with each of the associations.

8.3 BROAD-SPECTRUM BENEVOLENCE OF SPICES AND HERBS

The category level study of disease associations for spices revealed that culinary spices and herbs positively affect a range of disease categories. To specify, we found that most spices in our dictionary show health benefits towards a wide range of MeSH disease categories. This combined with the fact that the positive health benefits far outnumber the negative effects, motivated us to device a metric to quantify the health impact of a culinary spice across disease categories. To quantify the broad impact a spice may have across diverse disease categories as well as sub-categories, we devised a 'spectrum score (Ω_s)'. The 'spectrum score of a spice (Ω_s)' encodes the diversity of adverse (Ω_s^-) or therapeutic (Ω_s^+) effects of a spice s across the MeSH disease categories as well as their constituent subcategories, and is defined as:

$$\Omega_s = \widehat{D}_s \cdot \sum_i^D \hat{d}_s^i / d^i \quad (8.1)$$

Here, D is the total number of MeSH disease categories, $\widehat{D}_s$ represents the number of disease categories with which spice s has therapeutic association with, d^i represents the total number of disease sub-categories in the ith disease category, and $\hat{d}_s^i$ represents the number of disease subcategories in the ith disease category with which the spice s is associated. When calculating the 'spectrum scores' across all 27 categories, the 'adverse spectrum score' and 'benevolent spectrum score' vary between 0 and 729. Further, for each spice the 'relative benevolence' $\Delta\Omega_s$ that encodes its residual therapeutic benefit was computed:

$$(\Delta\Omega_s = \Omega_s^+ - \Omega_s^-) \quad (8.2)$$

This metric computes the sum of the proportion of disease terms associated with a spice at the second level of MeSH hierarchy (sub-categories), multiplied by the number of disease terms associated at the first level (categories). With 27 disease categories, the lower and upper bound for the spectrum score is 0 and 729 respectively. To elucidate further, let us consider a spice that is associated with all diseases in exactly half of the MeSH disease categories versus another spice that has associations with half of the diseases in every disease category. In such a case, the latter would have a higher spectrum score than the former. We computed the spectrum score for both positive (benevolence spectrum score, Ω_s^+) as well as negative associations (adverse spectrum score, Ω_s^-).

The spices with highest 'benevolence spectrum score' according to our analysis were garlic (*Allium sativum*), ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), liquorice (*Glycyrrhiza glabra*), ginkgo (*Ginkgo biloba*), black cumin (*Nigella sativa*), cinnamon (*Cinnamomum verum*) and saffron (*Crocus sativus*) whereas the top adverse spectrum spices were liquorice *(Glycyrrhiza glabra),* ginger *(Zingiber officinale),* fenugreek *(Trigonella foenum-graecum),* ginkgo *(Ginkgo biloba),* sunflower *(Helianthus annuus)* and *Celery (Apium graveolens).* Spices such as garlic, liquorice and ginkgo have a high benevolence as well as adverse spectrum scores.

We found that for 150 out of 152 spices, the 'benevolence spectrum score' exceeded the 'adverse spectrum score', with almost 50 spices having 'relative benevolence' ($\Delta\Omega_s$) greater than 50 (Fig 8.3). Hence, it may be concluded that, in general, spices have positive effects with a broad spectrum of diseases in contrast to their negative effects, which are comparatively narrow-spectrum. In line with our analysis, spices have been reported to be effective against a range of disorders [Kaefer and Milner, 2008; K. Srinivasan, 2005; Krishnapura Srinivasan, 2005b, 2017]. Details of benevolent, adverse as well as relative benevolence scores for all spices are provided online on supporting information linked to [Rakhi et al., 2018].

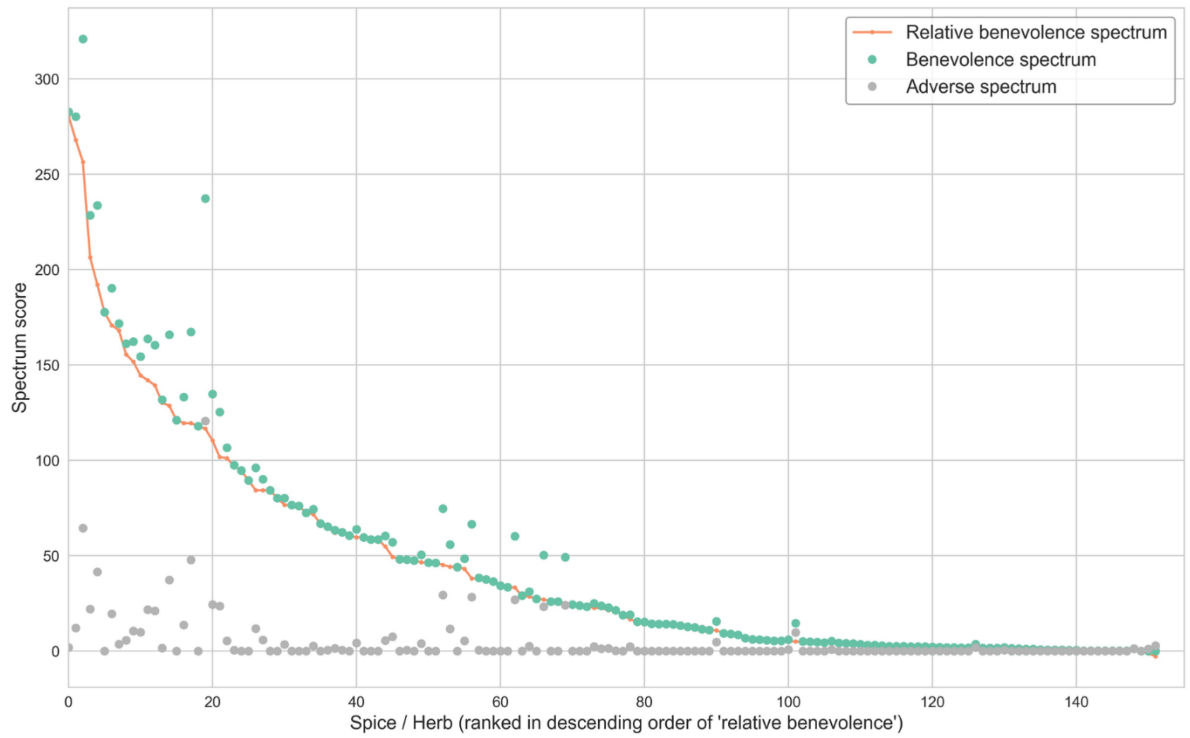

Figure 8.3: Spices ranked according to their 'relative benevolence score', highlighting their broad-spectrum benevolence. This score enumerates the relative health benefits as reflected in the difference between the 'benevolence spectrum' and 'adverse spectrum' scores. Barring two, all spices had positive scores with a large number of them showing significantly larger therapeutic effects compared to their adverse effects.

8.4 CULINARY RECOMMENDATIONS

Each of the MeSH disease categories refers to a class of disorders such as nutritional and metabolic disorders, cardiovascular diseases, nervous systems diseases, digestive system diseases, immune system diseases, neoplasms, bacterial infections and mycoses, virus diseases and such. We formulated a way to recommend spices and herbs for each of these MeSH disease categories by sorting them according to their relative significance. This means that we prioritize certain spices and herbs having for a particular disease category by looking at their relative positive and negative benevolence. The 'spectrum score' forms the basis to prioritize spices for culinary intervention against a MeSH disease category. We computed the category-specific 'benevolence spectrum' and 'adverse spectrum' scores to enumerate the 'trade-off score' that represents the therapeutic value of a spice against a class of disorders. The complete list of culinary recommendations intended as a dietary intervention against various disease categories can be found online under supporting information linked to [Rakhi et al., 2018]. Category-specific (benevolence and adverse) spectrum score was defined as:

$$\Omega_s^i = \hat{d}_s^i \cdot \sum_k^{d^i} \hat{\alpha}_s^k / \alpha^k \tag{8.3}$$

Here, $\hat{d}_s^i$ represents the number of disease sub-categories in the ith disease category with which spice s has therapeutic association with, α^k represents the total number of diseases in the kth disease sub-category, and $\hat{\alpha}_s^k$ represents the number of disease subcategories in the kth disease sub-category with which the spice s is associated. The 'therapeutic tradeoff score', $\Delta\Omega_s^i$, represents the difference between the 'benevolence spectrum' and 'adverse spectrum' of spice s for category i; the higher the tradeoff score of a spice, the better is its therapeutic value against the spectrum of diseases represented by this category. Thus, the tradeoff score of a spice serves as a basis for its recommendation against a MeSH disease category.

Empirical evidence for the recommendations provided by our study can be found in the literature. Our data suggest that spices show therapeutic effects against most of the viral diseases. Among them, turmeric (*Curcuma longa*) is the most broad-spectrum antiviral spice and is reported with inhibitory properties against various viruses, including HIV, influenza, and coxsackievirus [Zorofchian Moghadamtousi et al., 2014]. Studies in human and animal models have shown that dietary spices significantly stimulate the activities of digestive enzymes of the pancreas and small intestines such as pancreatic lipase, amylase and proteases thereby acting as digestive stimulants. Spices like ginger and garlic stimulate TRPV1, a sensor in the digestive system which has implications for gastrointestinal tract pathology and physiology [Holzer, 2011; Platel and Srinivasan, 2004]. Prominent spices recommended for cardiovascular diseases, such as tulsi (*Ocimum tenuiflorum*), mint (*Mentha X piperita*), ginkgo (*Ginkgo biloba*) and ginger (*Zingiber officinale*), have been reported with beneficial effects against cardiovascular disorders. Epidemiological studies suggest that these spices lower cholesterol levels, decrease platelet aggregation, reduce blood pressure, and increases antioxidant status which in turn decreases the progression of cardiovascular diseases [Rahman and Lowe, 2006]. Black cumin (*Nigella sativa*), turmeric (*Curcuma longa*) and garlic (*Allium sativum*) are prominent spices recommended for diabetes, a major metabolic disorder. Evidence from animal studies and human trials have indicated that these spices modulate hyperglycemia and lipid profile function. Their antioxidant characteristics and effects on insulin secretion, glucose absorption, and gluconeogenesis make them potent candidates towards treating diabetes [Bi, Lim, and Jeyakumar Henry, 2017; Heshmati and Namazi, 2015]. Similarly, the anti-diabetic property of ginkgo (*Ginkgo Biloba)* may be linked to the ability of its extract to reduce insulin resistance.

Incidentally, the spices that frequent in the culinary recommendations are among those used for culinary and medicinal preparations across cultures. Curcumin (*Curcuma longa*) and tulsi (*Ocimum tenufloreum*), widely used in Indian culinary and medicinal preparations, were present across recommendations made throughout the spectrum of MeSH disease categories. Similarly, garlic, used in Southern European especially Italian cuisine, also appeared in culinary recommendations across all categories of diseases. Some of the other most potent spices include ginger (*Zingiber officinale*), black cumin (*Nigella sativa*) and ginkgo (*Ginkgo biloba*) (see Annexure Table C.2)

8.5 DISCUSSION

Humans are unique in having developed the ability to cook, which has been argued to be critical for the emergence of their large brains [Fonseca-Azevedo and Herculano-Houzel, 2012; Wrangham, 2009]. While cooked food must have provided with much-needed energy supply, it is intriguing that they flavor the food with nutritionally insignificant quantities of herbs and spices. Going beyond the ability of spices to act as a flavoring and antimicrobial agents [Billing and Sherman, 1998], our analysis of spice-disease associations text-mined from biomedical literature shows the broad-spectrum benefits of spices. Recent studies have shown the potential benefits of consumption of spices such as chillies through cohort studies [Chopan and Littenberg, 2017] as well as the role of specific spice phytochemicals in their health effects [Jiang et al., 2017]. Interestingly, the broad-spectrum benevolence score of a spice was not positively correlated with its phytochemical repertoire (Annexure C.1.3), suggesting that richness in the phytochemical content itself does not explain its therapeutic value.

We also point out adverse health effects of spices, largely reflected in allergies, immune system and skin-related disorders. Few of the negative effects of spices have been linked with their excessive use. For example, liquorice, a beneficial herb for hypertension, can cause weight loss, hypokalemia and other related adverse effects if consumed in large doses. Beyond probing the molecular basis of positive associations, it would also be of interest to identify toxic phytochemicals present in spices and assess their effect on specific diseases to provide an advisory against their consumption. Negative associations for spices projected by our study can serve as a basis for such investigations.

As opposed to a previous attempt in this direction [Jensen, Panagiotou, and Kouskoumvekaki, 2014; Jensen et al., 2015] that linked all plant-based foods with diseases and phytochemicals from literature, our study focused on culinary spices and herbs. We investigated an exhaustive dictionary of 188 culinary herbs and spices with far better coverage (99 additional) than that of NutriChem [Jensen et al., 2014, 2015]. Overall, in terms of the number of disease associations, the depth of our analysis was better than that of NutriChem [Jensen et al., 2014, 2015] (Annexure C.1.1) and our data comprised a broader set of associations for most spices (Annexure C.1.2). NutriChem [Jensen et al., 2014, 2015] used a dictionary-based string matching approach for named entity recognition and normalization of diseases as well as plants. In the case of diseases, it is empirically shown that depending on the disease dictionary used, the string matching approach typically leads to a low precision and recall [Li et al., 2016]. We used TaggerOne [Leaman and Lu, 2016], a machine learning-based named entity recognition tool which yields state of the art performance. Even though the performance of our relationship extraction model was evaluated on a dataset consisting of positive, negative and neutral associations in contrast to previous studies that evaluated on only positive and negative associations, our model achieves a comparative F1 score. In addition to this, we provide accurate information about the adverse effects of spices by manually correcting all predicted negative associations. Despite our best efforts to ensure accurate extraction of spice-disease associations, our method is constrained by shortcomings inherent to text mining approaches and the use of limited information pertaining to biomedical literature, namely, title and abstract. Overall, our analysis serves as a precursor to systematic reviews including meta-analysis as well as hypothesis-driven investigations into the health effects of spices and herbs.

Similar to languages where words are synthesized from the same phonetic repertoire, cuisines around the world have concocted their own unique ingredient combinations, especially those made from spices [Jain et al., 2015a, 2015b]. Interestingly, many cuisines around the world such as those from the Indian subcontinent (*paanch phoron*, *garam masala*, *sambar masala* among a host of others referred to as *masala*), Ethiopia (*berbere*) and Middle East (*baharat*) to mention a few, have ended up developing unique spice combinations of their own. It remains to be critically examined whether these have been deliberately composed with an appreciation of therapeutic properties of spices and herbs, or are accidentally emerged constructs. Spices are frequently used as part of functional foods, for example, the Indian dish *rasam* is a concoction of different spices and has been reported to be hypoglycemic, anti-anemic and antipyretic [Devarajan and Mohanmarugaraja, 2017]. *Sambar*, another predominantly spice-based recipe, has been shown to work against prostate cancer [Prasad et al., 2016]. Traditional medicinal systems are also known to recommend spices as part of their prescriptions. *Trikatu* [Doss, Ganesan, and Rasool, 2016], a spice concoction made with black pepper, long pepper, and dried ginger has been advised to be of value against rheumatoid arthritis by Ayurveda, a classical traditional medicinal system from India. In Chinese traditional medicine, *Xiaoyao-san*, a combination of various spices, has been recommended for the management of stress and depression-related disorders [Liu et al., 2017].

Cooking typically involves high-temperature processing via heating, boiling, frying and such. It could be argued [McGee, 1998] that heating is a simpler and more effective means of killing microbes, thereby refuting the antimicrobial hypothesis [Billing and Sherman, 1998]. Other beneficial effects of spices (such as anti-diabetic, anti-carcinogenic and antioxidant and inflammatory), unearthed in this study, could not be argued against with this logic. Ironically, this argument raises another critical question: Whether the therapeutic properties and bioactivity of spice phytochemicals can sustain the intense heating processes typically involved in cooking [Suresh, Gurudutt, and Srinivasan, 2009]? Besides that, one of the ambiguous factors in appreciating the benevolence of spices is the distinction between the effectiveness of individual compounds vis-à-vis their synergistic actions. Apart from these aspects, there is ample scope for improvising the strategy for culinary recommendations as well as for identifications of molecular mechanisms involved in the health impact of spices by including the data of quantity and disease-specific potency of their constituent phytochemicals. While raising a host of such critical questions related to dietary intake of herbs and spice and by investigating the evidence from biomedical literature reporting health effects of culinary herbs and spices our data-driven analysis suggests their broad-spectrum benevolence.

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