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31

32 **Abbreviations:** Complementary and Alternative Medicine (CAM), American Academy
33 of Allergy, Asthma, and Immunology (AAAAI), Dietary Supplement and Health
34 Education Act (DSHEA), Food and Drug Administration (FDA), United States
35 Pharmacopeia (USP), National Sanitation Foundation (NSF), Diamine oxidase (DAO),
36 glycyrrhetic acid (GA), 11- β -hydroxysteroid dehydrogenase (11 β HSD), pyrrolizidine
37 alkaloids (PA)

38

39 **Abstract**

40 Natural products are a category of complementary and alternative medicine that include
41 medicinal plants, vitamins and dietary supplements. These products are often utilized by
42 patients with allergies in conjunction with, or as an alternative to, their conventional
43 medical therapies. Despite the wide use of these modalities, many clinicians often have
44 limited knowledge and training in their use. It is important for health care providers to
45 know the safety and risks of these products that their patients may use. This *Clinical*
46 *Commentary* reviews the side effects and adverse reactions of several natural products
47 commonly used by patients with allergies and gives an overview of the FDA
48 requirements for manufacturing, advertising and distribution.

49

50 **Introduction**

51 Natural products are a category of complementary and alternative medicines (CAM) that
52 fall under a broader classification that the National Center for Complementary and
53 Integrative Health defines as “Nutritional Approaches”; they include herbs, vitamins, and
54 supplements¹. The products have become commonplace in the American health and
55 wellness culture and can be found on the shelves of pharmacies, supermarkets, and
56 farmers markets alike. Americans spend 12.8 billion dollars annually on these products,
57 with a mean annual out-of-pocket expenditure of \$368². As per the 2012 National
58 Health Interview Survey, natural products are used by 33% of adults³. More recent data
59 from the National Health and Nutrition Examination Survey reported that 57.6% of US
60 adults aged 20 and over have used a dietary supplement in the past 30 days².

61
62 According to allergists surveyed, almost 90% of allergy patients using CAM are
63 motivated by a desire to use, what they deem to be, more natural interventions.⁴
64 Patients preference for these interventions is often attributed to distrust in the
65 relationships between pharmaceutical companies and physicians⁵. Although ‘natural’ is
66 often conflated with ‘safe’, adverse reactions can occur with these products⁶ with an
67 estimated 23,000 yearly emergency room visits attributed to adverse reactions,
68 including allergies ⁷. However, this represents only 1.8% of all ED visits for adverse drug
69 events, so relative to prescription medications, this number is quite low⁸. A 2013 survey
70 by the AAAAI revealed that almost 60% of allergists have seen adverse reactions to
71 CAM ⁴. It is important for clinicians to understand both the safety and risks of natural
72 compounds, as well as governmental oversight of these products.

73 In 1994 the Dietary Supplement and Health Education Act (DSHEA) defined the term
74 “dietary supplement” and set guidelines for manufacturers⁹. Dietary supplements
75 include: vitamins, minerals, herbs, other botanicals, amino acids and “dietary
76 substances” that are part of food items (e.g., enzymes and probiotics). They are not
77 considered to be drugs or food, and thus are not beholden to many of the same rules
78 and regulations(*Table 2*)⁹. According to the DSHEA, unlike drugs, these products can
79 be marketed without evidence of safety or efficacy (the exception being supplements
80 containing novel dietary ingredients that are not normally present in the food supply).
81 The manufacturer is not required to report adverse events to the FDA, and the burden
82 of proof is on the FDA to demonstrate that the product is unsafe before legal actions
83 can take place. ⁹ These over-the-counter products can often be illegally adulterated;
84 recently, the FDA detected sildenafil in certain erectile dysfunction products, anabolic
85 steroids in muscle growth supplements, and sibutramine in weight loss supplements.¹⁰

86 The DSHEA also set guidelines that prohibit making claims to prevent, treat or cure
87 specific illnesses. However, manufacturers are permitted to make broader health claims
88 as long as the label includes: “This statement has not been evaluated by the Food and
89 Drug Administration. This product is not intended to diagnose, treat, cure, or prevent
90 any disease.”⁹ Improved regulation of quality and assurance of accurate ingredient
91 content would better protect the consumer. Without oversight, the consumer is at the
92 mercy of the manufacturer.

93 To remedy this, many manufacturers use external, private certification services to assay
94 and confirm quality and quantity of active ingredients. The certifiers are nationally
95 recognized, and include the United States Pharmacopeia (USP), which certifies

96 pharmaceuticals, and the National Sanitation Foundation (NSF)¹¹. Manufacturers pay a
97 fee for each individual product certified and are then allowed to display the certification
98 seal on the product label¹¹. While these companies provide a much needed and
99 valuable service these fees can also be prohibitive to smaller manufacturers.

100

101 CAM is loosely defined as those healthcare interventions that exist outside of the
102 mainstream of conventional medical practice. Integrative medicine is distinct from CAM
103 by grounding itself in the purposeful coordination of these modalities by the
104 conventional medical care team¹ (*Table 1*). Eighty-one percent of allergists report
105 having encountered patients opting to use CAM interventions in lieu of conventional
106 approaches⁴. In spite of the prevalent use of CAM, non-disclosure rates reach 77%¹².

107

108 Navigating natural products presents many challenges for the practicing allergist, but it
109 is prudent that they familiarize themselves with these interventions in order to best care
110 for their patients who prefer such approaches. Unfortunately, research on natural
111 products is often limited making it a challenge for practitioners who appropriately insist
112 upon a strict evidence-based approach to guide their patients using them. This review is
113 intended to give an overview of some of the recognized, both clinical and potential
114 adverse reactions from natural products often utilized by allergic patients.

115

116 **Specific Herbs/Herbs Supplements (Table 3)**

117

118 **STINGING NETTLE**

119 Stinging nettle is an herbaceous, perennial, flowering plant with hair-like projections
120 along its leaves¹³. Its Latin name *Urtica dioica* shares similar etymology to urticaria,
121 due to its ability to induce hives upon skin contact with these projections. Interestingly,
122 these projections contain histamine, serotonin, and acetylcholine, all of which are
123 associated with allergic disease¹⁴. Traditionally, stinging nettle has been used as an
124 anti-hypertensive, to treat muscle and joint pain¹⁵ and as a galactagogue¹⁶. Recent
125 research also suggests a role in glycemic control¹⁷.

126
127 The use of stinging nettle in allergic rhinitis has been studied using both freeze-dried
128 leaf¹⁸ and root extract preparations¹³. The anti-allergy effect is believed to be
129 secondary to quercetin (see below).¹⁹ *In vitro* work demonstrated antagonist and
130 negative agonist activity against H1 receptors, and the inhibition of mast cell tryptase.
131 Anti-inflammatory effects on COX-1 and COX-2 have also been demonstrated²⁰.

132
133 Two randomized controlled studies examined the potential benefit of stinging nettle on
134 allergic rhinitis. Two of 31 patients receiving nettle experienced worsening of allergic
135 symptoms, and several patients developed mild gastric discomfort.¹⁸ Bakhshae, et
136 al. reported, that of the 35 patients in the intervention arm “no serious, deleterious
137 adverse effects” were observed. ¹³ Stinging nettle has been studied in the management
138 of glycemic control¹⁷, therefore caution should be exercised when using it in
139 conjunction with medications that may lower blood sugar, although no hypoglycemia
140 has been reported. Not surprising, given its historical use as a galactagogue, there
141 have been several cases reported of gynecomastia, hypoestrogenism and

142 galactorrhea²¹⁻²². While murine models have demonstrated interference with the
143 cytochrome P450 pathway²³ the clinical relevance of this remains unclear.

144

145 Finally, topical use of stinging nettle should be avoided, given the risk of urticaria, with
146 a single case in the literature of severe tongue angioedema after ingesting uncooked
147 nettle²⁴.

148

149 QUERCETIN

150 Quercetin is a member of the flavonoid family, a group of plant-derived compounds
151 recognized for their anti-oxidative properties. It occurs naturally in a multitude of fruits
152 and vegetables including, onions asparagus, broccoli and berries²⁵. It is also found in
153 herbs such as St. Johns Wort²⁶ and elderberry²⁷. As mentioned above, it is found in
154 stinging nettle and hypothesized to be the active constituent in its potential benefit in
155 treating allergic rhinitis.

156

157 In vitro studies and animal models suggest that quercetin impacts atopic disease
158 through a number of mechanisms including suppression of mast cell activation,
159 histamine release and suppression of eosinophilic inflammation as well as helping to
160 prevent a Th2 skew^{25,28}.

161

162 Clinical studies using oral quercetin in allergic disease are scant, but two studies—one
163 involving children²⁹ and the other with adults³⁰—used a product that also included
164 *Perilla frutescens* extract and vitamin D3. In the pediatric study, no serious adverse

165 events were reported, but 50% of patients in the treatment arm did experience adverse
166 reactions, versus 36% in the control arm. Unfortunately, the authors did not detail these
167 adverse reactions.

168
169 In a small study of 17 patients examining its benefit in prostatitis one subject reported
170 mild paresthesia and another reported headache, both of which resolved upon
171 cessation of treatment³¹. Subjects using quercetin (n=44) following myocardial
172 infarction³² and those with chronic obstructive pulmonary disease (n=6)³³ reported no
173 adverse reactions. In vitro studies demonstrated inhibition of CYP3A4 and CYP2C19
174 in human liver microsomes³⁴ and CYPs 1A1 and 3A4 in human intestinal Caco-2 cells³⁵
175 but the clinical relevance of these findings is unknown.

176

177 DAO - Diamine Oxidase

178 Histamine intolerance is a popular, yet theoretical, physiologic response to both
179 excessive endogenous and exogenous histamine sources³⁶. Symptoms are non-
180 specific, including facial flushing, dizziness, nausea, diarrhea and brain fog³⁷ and are
181 largely attributed to foods with high histamine content or medications that may inhibit
182 the activity of diamine oxidase³⁸. Diamine oxidase is the enzyme responsible for
183 degradation of extracellular histamine within the body and theorized to be deficient in
184 patients with histamine intolerance³⁶. While the diagnosis of histamine intolerance is
185 controversial, it is often made by alternative medicine practitioners, and a supplement
186 form of diamine oxidase is commonly prescribed to help manage symptoms. DAO
187 supplements are most commonly prepared using porcine kidney concentrate³⁹ but

188 vegetal sources such as Indian Pea (*Lathyrus sativus*)⁴⁰ are also commercially
189 available.

190
191 When studied in subjects with migraine and DAO deficiency, no adverse effects were
192 'registered' in patients treated with the enzyme supplement⁴¹. Two small interventional
193 studies using a DAO supplement—one in patients with 22 symptoms associated with
194 histamine intolerance (n=35),⁴² and another in patients with chronic spontaneous
195 urticaria(n=20)⁴³— did not report adverse reactions.

196
197 ECHINACEA

198 Echinacea (coneflower) is a perennial flowering plant part of the Asteraceae family. It is
199 indigenous to the Rocky Mountains and was traditionally used by Native Americans⁴⁴.
200 Commercial preparations of echinacea tend to be quite heterogenous in their
201 preparation, parts of the plant used, and even in the exact species used⁴⁵. Three
202 separate species of Echinacea, *E. angustifolia*, *E. purpurea*, and *E. pallida* can be found
203 commercially⁶.

204
205 Echinacea is not generally used in the management of atopic disease, but it remains
206 one of the most commonly purchased botanical supplements. It is often used in the
207 management of upper respiratory infections⁴⁵ which are difficult to distinguish from
208 allergic rhinitis. In fact, 38% of allergists report that their patients use Echinacea.⁴

209 Due to its cross reactivity to its fellow member of the Asteraceae family Echinacea can
210 pose a theoretical risk to the allergic patient—especially those with preexisting

211 sensitizations to other members such as ragweed. There have been prior reports in the
212 literature of anaphylaxis to echinacea^{6,46} but given the prevalence of echinacea use, this
213 risk is likely low. Echinacea is generally well tolerated in both adults and children⁴⁷

214

215 LICORICE ROOT

216 Licorice root (*Glycyrrhiza glabra*) is a botanical with a history of ancient use by
217 herbalists and traditional Chinese medicine practitioners that was adopted as a
218 conventional medical therapy nearly 75 years ago⁴⁸. Historically, licorice root extracts
219 were used as anti-inflammatories in the treatment of respiratory infections and gastric
220 ulcers that predates the Egyptian and Babylonian empires⁴⁹. In the late 1940's, it was
221 noted that approximately 20 percent of patients treated with licorice root developed
222 mineralocorticoid side effects, including hypertension and edema⁴⁸. Careful evaluation
223 of these patients revealed a desoxycorticosterone acetate (DOCA)-like activity⁴⁸—one
224 that mimicked the activity of the recently described adrenocortical hormones. This
225 steroidal activity was verified when patients with Addison's disease were successfully
226 treated using licorice root extract in the early 1950's⁴⁸. Within a decade, more potent,
227 synthetic corticosteroids replaced licorice root as a treatment of adrenal insufficiency
228 and as an anti-inflammatory.

229 The mechanism of action of several compounds contained in licorice root extract was
230 elucidated in the 1980's. Two primary active components of licorice root extract,
231 glycyrrhizic acid and glycyrrhetic acid (GA), have been shown to inhibit the activity of
232 11- β -hydroxysteroid dehydrogenase (11 β HSD), an enzyme that catalyzes the
233 conversion of the active steroids cortisol (hydrocortisone) and corticosterone to the

234 inactive compounds cortisone and 11-dehydrocorticosterone⁵⁰. Inhibition of 11 β HSD
235 leads to an accumulation of active corticosteroids, by inhibiting steroid metabolism. This
236 mechanism is implicated in the potential benefit of licorice in treating asthma⁵¹

237 In terms of adverse effects, licorice root can occasionally cause a state of excess
238 mineralocorticoid activity (or pseudohyperaldosteronism) that can lead to increases in
239 blood pressure, edema, and occasionally hypokalemia. This is typically much rarer than
240 effects seen with systemic corticosteroids, however monitoring of blood pressure and
241 potassium levels are recommended.

242

243 BUTTERBUR

244 Butterbur (*Petasites hybridus*) has a long history of use for migraine prophylaxis,
245 however there is also a small body of evidence supporting its use in allergic and
246 respiratory diseases^{52,53}. The leaf and root are commonly used in preparations of the
247 butterbur extract, which is typically standardized based upon petasin and isopetasin
248 concentrations. Extracts inhibit the formation of cyclooxygenase, leukotrienes and
249 histamine⁵⁴.

250

251 The butterbur plant in its natural state contains pyrrolizidine alkaloids (PA's) which have
252 been causally linked to liver cancer, so no raw, unprocessed preparations should ever
253 be used⁵⁴. Care should be taken to ensure that the butterbur extract used is free of all
254 detectable PA's. In addition, there is a potential for cross reactivity in patients with
255 ragweed sensitivity, but no documented cases have been published.⁵⁵.

256

257 FISH OIL

258 Essential fatty acids have been the subject of study for decades. Their supplement use
259 was popularized in the late 1970s when Danish researchers determined that members
260 of the Intuit population in Greenland had a significantly delayed death rate from acute
261 myocardial infarction, relative to matched individuals in Denmark⁵⁶. The researchers
262 concluded that high levels of omega-3 fatty acids in the fish-based diet of the Intuit were
263 responsible for this difference.

264
265 Since that time, hundreds of *in vitro* and *in vivo* studies have examined the effect of high
266 or low dietary omega-3 ingestion on dozens of conditions, including asthma. *In vitro*
267 stimulation of neutrophils from asthmatic patients supplemented with fish oil showed
268 reduced arachidonic acid release by over one-third and inhibited 5-lipoxygenase
269 products by nearly 50% has been demonstrated ⁵⁷ .

270
271 There are few adverse effects noted with fish oil. The absence of parvalbumin in
272 molecularly distilled and pharmaceutical-grade preparations make fish oil even safe for
273 those with finned fish-allergic individuals⁵⁸. Many people experience mild nausea
274 following ingestion of fish oil, which is readily mitigated by storing the fish oil in the
275 freezer and taking the capsules frozen. There were some reports of an increased
276 frequency of cardiac arrhythmias in individuals taking high-dose fish oil as part of a
277 study⁵⁹⁶⁰, but this has not been uniformly seen⁶⁰. Caution should be exercised when
278 using fish oil along with anticoagulation therapy, as bleeding time may be increased.
279

280 CURCUMIN (TURMERIC)

281 Curcumin (*Curcuma longa*) is a polyphenol that has been shown to have anti-
282 inflammatory properties with broad use in autoimmune, intestinal, and neoplastic
283 disorders⁶¹. Its use has been supported in various atopic conditions including allergic
284 rhinitis and asthma^{62,63}. Extracts of the root are commonly used in supplements and as
285 a dietary herb.

286

287 Adverse reactions to curcumin have been reported in the literature, though appear to be
288 rare⁶¹. Hypersensitivity reactions, including anaphylactoid reactions, have been
289 described but true anaphylaxis is a rare occurrence.^{64,65} Moreover, a handful of case
290 reports of contact allergic dermatitis have appeared in the literature as well as at least
291 two cases of contact urticaria^{66,67,68,69} While infrequent, skin hypersensitivity reactions
292 are a possible side effect of topical preparations.

293

294 Metal toxicity is a theoretical concern with curcumin use due to associated cobalt-
295 binding properties⁷⁰ and speaks to quality sourcing. Case reports of hepatotoxicity related
296 to curcumin exist, usually in conjunction with other treatments such as chemotherapy⁷¹.
297 Reports of hepatotoxicity with curcumin were hypothesized due to the presence of
298 heavy metals, chromate, illegal dyes, non-steroidal anti-inflammatory agents, and
299 pyrrole alkaloids but not proven in a 90-day prospective study of a curcumin compound
300 containing 380mg of daily curcuminoids⁷².

301

302 Curcumin has been touted for its antiplatelet properties which may be beneficial in
303 specific settings⁷³. However, understanding the impact of these physiologic properties is
304 important. Tetrahydrocurcumin (THC), the active metabolite of curcumin has been
305 shown to attenuate platelet generation offering cardioprotective benefits therefore there
306 is theoretical concern of bleeding risk, however no impacts on surgical bleeding risk
307 have been reported⁷⁴.

308

309 GINGER

310 Ginger (*Zingiber officinale*), is a traditional spice that has been long touted for its anti-
311 inflammatory and anti-viral properties⁷⁵. It has favorable effects as an anti-emetic with
312 application in digestive disorders as well as potential benefit in allergic rhinitis, asthma
313 and other respiratory conditions.

314

315 The side effect profile is limited. Reactions to ginger can vary from hypersensitivity to
316 physiologic effects. As a common spice in the occupational setting, contact dermatitis
317 reports are known to exist in the literature but lacking in standardization and
318 qualification^{76,77}. IgE-mediated hypersensitivity reactions to ginger are not commonly
319 reported in the medical literature though have been described⁷⁸. Though considered in
320 the same family as curcumin, no cross-reactivity of allergenicity has been reported.
321 Moreover, the overall safety profile of ginger is favorable across many studies related to
322 systemic disease though reflux symptoms have been reported⁷⁹. Finally, toxicity
323 related to heavy metals or toxic compounds remains a concern of herbal supplements in

324 the medical community⁸¹, and even though not substantiated, speaks to the importance
325 of sourcing, ultimately favoring use of the natural product where possible.

326

327 Bleeding risk and hypoglycemia have been postulated but there is no medical literature
328 to predict or estimate this risk. A small randomized double-blind, placebo-controlled
329 study of eight healthy males revealed no effect of up to 2g of dried ginger powder on
330 bleeding time or platelet function⁸². With respect to hypoglycemia this may be beneficial
331 as a potential therapeutic in diabetic patients, though hypoglycemic effects have been
332 demonstrated in normoglycemic murine models and would require further study in the
333 general population for further application ⁸³.

334

335 PROBIOTICS

336 Probiotics is a broad term, used to categorize microorganisms used as supplements to
337 support the microbiome. Given the plethora of different probiotic strains and
338 formulations of probiotics on the market it is challenging to speak to each individually
339 but it is important to understand potential exposures to hidden allergens including
340 lactose and cow's milk and soy. Similar to the understanding of excipients of lactose in
341 medications, there is plausible risk of hypersensitivity in suspected individuals and
342 children⁸⁴. A small study examined probiotics labeled with and without lactose and
343 discovered that in addition to cow's milk protein, hen's egg protein was also identified,
344 potentially putting those with a history of anaphylaxis to these foods at risk⁸⁵. In a large
345 double-blind, placebo-controlled randomized study of pregnant women with eczema
346 receiving different strains of probiotics, only a single patient on treatment demonstrated

347 an exacerbation of eczema suggesting that hypersensitivity responses in an otherwise
348 susceptible population is uncommon ⁸⁶. Although rare, checking labels to ensure they
349 do not contain cow's milk, soy or other allergen products is good practice. While
350 probiotics can be found in dairy-rich foods such as yogurt or kefir, this is not to say that
351 all probiotics supplements contain dairy. Thus it is important to recognize that
352 lactobacillus as a common active bacteria in dairy preparations is not the same and
353 should not be mistaken for lactose. In addition the bacillus component in a particular
354 strain did not correlate with specific toxins related to the bacteria during in vitro
355 analysis⁸⁷. Sourcing of probiotics and regulation of probiotics to specify exact colony
356 forming units (CFUs) remains a challenge and potential limitation of their use⁸⁸

357

358 The most common side effects of probiotics in patients with atopic disease are
359 gastrointestinal complaints, including abdominal pain, diarrhea and flatulence, though
360 not necessarily more than placebo and rarely resulting in discontinuation of therapy ^{89,86}.
361 Furthermore, in post-partum women with eczema taking probiotics and nursing,
362 gastrointestinal symptoms of the infants were noted in over 40%, but not significant
363 across probiotics and compared to placebo⁸⁶. However, in a cohort of 52 patients
364 receiving probiotics consisting of Lactobacillus and Bifidobacterium in chronic urticaria,
365 no adverse effects were reported though 14 patients withdrew for unrelated reasons ⁹⁰.
366 Given the broad use of probiotics in multiple disease states, systematic reviews do not
367 show significant adverse reactions and there has been no meaningful discontinuation of
368 probiotics due to side effects or reactions ⁹² Special populations in which to exercise
369 caution of common strains of probiotics are those who are immunocompromised,

370 critically ill, with chronic gastrointestinal issues, and extremes of age due to risk of
371 bacteremia, impaired gut health and rare but serious infectious complications⁹³.

372

373 VITAMIN D

374 Vitamin D is readily available both in prescription and over-the-counter forms for various
375 conditions, yet toxicity remains a serious, albeit rare, concern in modern clinical
376 practice. Vitamin D has been suggested as an adjunct therapy in the management of
377 asthma, especially in the case of steroid resistance in severe asthma⁹⁴. Dosing of
378 Vitamin D varies, and often obtained through diet including fortified sources. The
379 Institute of Medicine recommends that for most individuals up to the age of 70, no more
380 than 600 IU of daily Vitamin D are needed⁹⁵. Maximum doses allowed have not been
381 universally established but in the setting of Vitamin D deficiency, doses as high as
382 50,000 IU weekly are often indicated for short periods. However, long-term higher
383 dosing of Vitamin D may place an individual increased risk for toxicity and is not
384 recommended. Ranges of excess Vitamin D have been reported more than 150 ng/mL,
385 however, one study of adults found that levels as high as 80 ng/mL and 120ng/mL were
386 observed in 1% and 0.1% respectively, yet clinical signs of toxicity were still exceedingly
387 rare⁹⁶

388

389 Hypervitaminosis D may result in hypercalcemia and nephrocalcinosis in which patients
390 present with signs of fatigue, abdominal pain, and nausea. Of consequence, renal
391 failure and cardiac arrhythmias can ensue as a result of these metabolic effects.
392 Broader analysis of risks for toxicity focus on incorrect dosing regimens but also

393 incorrect manufacturing resulting in increased exposure and effects⁹⁷ The pediatric
394 setting may be particularly vulnerable to such errors thus requiring closer monitoring⁹⁸.
395 Nevertheless, Vitamin D replacement appears to be safe and beneficial when
396 indicated⁹⁹. In addition, drug-drug interaction of Vitamin D is occasionally a concern,
397 particularly with extremely high doses that may impact drugs that rely upon calcium
398 homeostasis.

399

400 CONCLUSION

401 The use of natural products is common among allergy patients, and it is important that
402 the practicing allergist educate themselves on these modalities as a means of both
403 nurturing the therapeutic relationship and being able to advocate for the safety and
404 success of their patients (*Table 4*).

405

406

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672

673 **Table 1: Glossary of Terms**

674

675 **Alternative Medicine:** Medical treatment modalities with emerging levels of evidence
676 used to treat illness in place of standard medical care.

677

678 **Complementary Medicine:** Medical treatment modalities with emerging levels of
679 evidence but often derived from traditional, ethnic or indigenous healing practices used
680 in conjunction with standard medical care.

681

682 **CAM (Complementary and Alternative Medicine):** A generic term used to group both
683 Alternative and Complementary therapies, typically used in place of standard medical
684 care.

685

686 **Integrative Medicine:** The judicious use of complementary modalities and standard
687 medical care in a collaborative and coordinated manner ideally overseen by a
688 practitioner with knowledge of both.

689

690 **Natural Products:** A category of treatments used in integrative medicine and CAM that
691 can include dietary supplements, herbs, vitamins, minerals, amino acids or live
692 microbials (ie probiotics).

693

694 **Dietary Supplement:** Compounds added to, or supplementing, standard nutritional
695 intake beyond food.

696

697 **Medicinal Herb:** Any plant or botanical used for the treatment or prevention of medical
698 illness. Different parts of the plant (ie flower, leaf, root) may be used for different
699 purposes.

700

701 **Vitamin** Organic substances required for normal cell development and function, but
702 typically unable to be synthesized by humans. Commonly found in foods, but also
703 available as dietary supplements.

704

705 **DSHEA Dietary Supplement and Health and Education Act of 1994**, is US federal
706 legislation that defined dietary supplements and enacted regulation of these products by
707 the FDA (though using a different set of regulations than those covering foods and drug
708 products).

709

710 **Table 2: Defining drug versus supplement**

Drug	Supplement
<p data-bbox="204 342 748 373"><u>Federal Food, Drug and Cosmetic Act</u></p> <p data-bbox="204 415 764 814">“intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”; “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”</p>	<p data-bbox="821 342 1271 447"><u>Dietary Supplement Health and Education Act</u></p> <p data-bbox="821 489 1421 961">A product intended to supplement the diet that contains one of the following ingredients: vitamins and minerals; herbs and other botanicals; amino acids; dietary substances that are part of the food supply, such as enzymes and live microbials</p>

711

712

713 **Table 3: Overview of supplements**

Supplement	Reported uses	Proposed mechanism of action	Reported Adverse Effects
Stinging nettle (<i>urticaria dioica</i>)	AR, asthma, diabetes	Mast cell stabilizer; decreased IFN-g, IL-6 and TNF-alpha	<i>Systemic:</i> Mild GI discomfort, Hypoglycemia, gynecomastia. <i>Topical:</i> Urticaria and angioedema
Quercetin	AR, asthma, inflammatory conditions, cancer prevention, anti-viral,	Mast cell stabilizer, COX-2 and NFKB inhibition, antioxidant	Nausea, vomiting, paresthesia,
DAO (diamine oxidase)	MCAS	Enzyme responsible for extracellular histamine degradation	No reported adverse effects
Echinacea (<i>E. angustifolia</i> , <i>E. purpurea</i> , and <i>E. pallida</i>)	Prevention of URIs	Inhibition of several inflammatory cytokines including TNF-alpha, and IL-6	Allergic reactions due to cross reaction to members of members of the Asteraceae family
Licorice root	Steroid-sparing agent; asthma; GERD; inflammatory conditions	Inhibits 11-B-HSD enzyme preventing endogenous CS degradation	Similar to CS. Pseudohyperaldosteronism; elevations in BP; edema; hypokalemia
Butterbur	Allergic rhinitis; migraines; sinus headache	Inhibits leukotriene and prostaglandin synthesis; decreases mast cell priming	Potential hepatotoxicity with some preparations containing pyrrolizidine alkaloids
Fish Oil	Asthma; CAD (1° and 2°); hyperlipidemia; inflammatory and rheumatologic conditions	Competes with omega-6 fats; inhibit synthesis of arachidonic acid, leukotrienes, and certain cytokines	Nausea; diarrhea; potential cardiac arrhythmias
Curcumin	AR, asthma, Inflammatory, rheumatologic, and neoplastic conditions	Polyphenol, anti-inflammatory and antioxidant; COX-1/COX-2 inhibition	<i>Systemic:</i> rare (anaphylactoid, metal toxicity 2/2 sourcing) <i>Topical:</i> discoloration, dermatitis/urticaria (rare)
Ginger	AR, URIs, GI related disorders	Antimicrobial, Anti-inflammatory, Anti-emetic	Overall, rare, such as hypersensitivity or physiologic (reflux, bleeding, hypoglycemia)

Probiotics	AD, AR, asthma and food allergies.	Immunomodulatory, Microbiome restoration	Abdominal pain, flatulence, diarrhea Caution in critically ill, GI patients, elderly/newborn infants Rare hypersensitivity reactions (if includes known allergens, ie cow's milk, soy)
Vitamin D	Broad applications, including pulmonary disease, severe and steroid-dependent asthma, AD and AR	Anti-inflammatory, Immunomodulatory	Vitamin D toxicity (often asymptomatic with increased levels): abdominal pain, fatigue and rarely, renal failure, cardiac arrhythmia

714 AD, Atopic Dermatitis; AR, Allergic rhinitis; CS, corticosteroids; GERD, Gastroesophageal
715 Reflux Disease; GI, gastrointestinal; IFN-g, Interferon gamma; MCAS, Mast Cell Activation
716 Syndrome; URI, Upper Respiratory infections.
717

718 **Table 4: Additional Resources to select quality supplements**

<p>Natural Medicine Database (https://naturalmedicines.therapeuticresearch.com/)</p>	<p>Highly annotated resource for examining available published evidence and indications for botanicals and supplements. It includes adverse reactions and recognized drug interactions</p>
<p>ConsumerLab (https://www.consumerlab.com/)</p>	<p>Performs independent testing of quality and purity of many retail products, and can be a useful guide to recommending specific brands or products. Product comparisons help consumers and healthcare professionals identify the best quality health and nutrition products.</p>
<p>AboutHerbs (https://www.aboutherbs.com)</p>	<p>Large compendium of herbs and supplements with primary focus on oncology. Sections built separately for clinicians and for patients.</p>