

Diet and Pemphigus

In Pursuit of Exogenous Factors in Pemphigus and Fogo Selvagem

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Individuals with a genetic predisposition to pemphigus will develop the disease only when one or more additional factors are present. The nature of these factors is as yet unknown, but our starting point was that certain drugs (penicillamine, captopril, and rifampicin) are recognized as such factors. Since some nutrients have chemical compositions similar to these known causative drugs, these nutrients may act similarly and, therefore, nutritional factors should also be suspected. As when drugs are involved, elimination of the inciting ingredients may be crucial for management of the disease. This article discusses the possible role of nutritional ingredients in the disease process of pemphigus, including fruit, leaves, roots, seeds, and even water. Possible causative candidates are thiol, thiocyanate, phenols, and tannins.

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Because the variability in the incidence and age of onset of pemphigus cannot be explained by genetics, environmental factors are implied. Susceptibility to autoimmune diseases is multifactorial¹; not all individuals with a proven susceptible genotype will develop autoimmunity. In many diseases, it appears that autoimmunity is preceded by some environmental insult. Tissue damage may be the key event that either allows for release of sequestered antigens from immunologically privileged sites or causes local inflammation resulting in lymphokine release and subsequent expression of antigens, or both. Sinha et al¹ note that perhaps the biggest challenge in the future will be the search for the environmental events that trigger self-reactivity.

It has been established that exogenous factors in the form of drugs, in particular thiol-containing drugs,^{2,3} play a role in the induction of pemphigus. This points to the possibility of finding other offenders, such as food products with chemical compositions similar to these drugs.^{4,9} We suggest that diet factors are involved in the pemphigus disease process and that, potentially, morbidity can be reduced if these factors are identified and avoided.

DIETARY FACTORS IN PEMPHIGUS

Thiol

When a thiol group is included in the molecular structure of a drug, the drug is capable of inducing pemphigus. Thiol groups are part of the molecular structure of certain plants; therefore, when these plants are ingested, they may have the same effects as thiol-containing drugs. Indeed, 3 compounds of garlic (allylmercaptan, allylmethylsulfide, and allylsulfide) were shown to induce acantholysis in vitro.⁵ Garlic belongs to the *Allium* group of plants, as do onion, shallot, chive, and leek, all of which also contain a thiol group. In the mountainous (Himalayan) zones of India there are many wild species of *Allium* L, and these appear at tribal markets.¹⁰ Evidence for involvement of thiol-containing foods in autoimmunity is provided by case reports indicating induction of pemphigus by garlic⁷ and leek.⁶ Elimination of these foods from the diet induced remission, and readministration caused exacerbation.

Isothiocyanates (Mustard Oils)

A distinct group of thiol-containing plants comprises those with thioglucosides— isothiocyanate-producing glucosides (by

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enzymatic hydrolysis). They are of the mustard family of plants that includes 3200 species in 375 genera and is of worldwide distribution.¹¹ Mustard (*Brassica nigra*) is a member of the Cruciferae family, as are horseradish, winter cress, turnip, broccoli (which contains both mustard oils, namely, isothiocyanates and allyl isothiocyanates), radish, cabbage, brussel sprouts, and cauliflower. The seeds of mustard (containing 30% fat) are used in French mustard, spices, and oils, and seed and root extracts yield allergenic mustard oils—isothiocyanates.¹² Depending on the chemical structure, the compounds are immunologically reactive (allyl and benzyl isothiocyanate) or irritants (phenyl isothiocyanate): they may either cause antibody-mediated acantholysis or be incorporated into the epidermis leading to nonimmunologic biochemical acantholysis in a manner similar to thiol-bearing drugs.¹³

The caper family (Capparidaceae), a tropical relative of the mustard family, is another source of thioglucosides.¹² Usually, several thioglucosides coexist in a single plant, and they are distributed throughout the plant in varying amounts during its growth cycle. Synthetic oil of mustard contains allyl isothiocyanate as the principal ingredient. Allyl isothiocyanate is widely used for flavoring of food products, especially seasoned sauces. It is an irritant to mucous membranes and produces blisters if left in contact with the membranes long enough.¹⁴

Phenols

Pemphigus may be topically induced as well: pemphigus erythematous has been induced by allergic contact dermatitis caused by tincture of benzoin,¹⁵ and contact with chromate has also caused pemphigus.¹⁶ The possibility of induction of pemphigus by contact with phenols has been described.¹⁷ Some phenolic compounds such as phenylisothiocyanate contain sulfur, and others do not. Following our previous publications,^{4,9} we received several letters from patients with pemphigus who experimented with foods and experienced variations in the symptoms of their disease with elimination or readministration of phenol-rich foods.

Urushiol. The mechanism by which urushiol elicits allergic contact dermatitis probably begins with covalent binding of the pentadecylcatechols to skin proteins.¹⁸ A similar reaction might be the first step in the sequence of events leading to acantholysis. Plants containing urushiol (3',5'-pentadecylcatechol) belong to the Anacardiaceae family that includes the genus *Toxicodendron* (poison ivy, poison oak, and poison sumac), the most prominent genus in causing allergic skin reactions. There are many related cross-reacting species such as mango,^{19,20} pistachio, and cashew that belong to the same family.

Other Phenolic Compounds. Aspartame, an artificial sweetener, is a phenolic compound, as are many other food additives such as preservatives, colorings, and flavorings. Sodium benzoate, tartrazine (yellow dye No. 5), vanillin, eugenol, caffeic acid, vitamins C and E, and cinnamic acid are all phenols. Cinnamic acid is present in apple, grape, orange, pineapple, and tomato juices. Cin-

namon spice is derived from the inner bark of *Cinnamomum zeylanicum*, the phenol-containing cinnamon tree, and many other species of *Cinnamomum* are also used as spices. Eugenol, for example, an oil distilled from *Cinnamomum* green leaves, is used as a flavoring for sweets and foods.

Pinene, another phenol-containing substance, is used to flavor baked goods, beverages, candy, condiments, chewing gum, and ice cream. It is also found in tomatoes, potatoes, mangoes, and bananas. Phenol-containing piperine constitutes 5% to 9% of the content of black pepper. Firewoods used for smoking and grilling foods are another source of phenol. Ingested phenolics are secreted in the milk and therefore appear in cows' milk. For example, gossypol is a phenolic constituent of cottonseed, and when cows are fed cottonseed, this fat-soluble compound appears in all the milk-fat products made from those cows' milk. Indole is another phenol found in milk.

Tannins

Tannins are naturally occurring plant polyphenolic compounds with considerable biologic activity. The astringency of many fruits during the early part of growth is due to high tannin content that declines as the fruit ripens. Certain woods, root materials, barks, leaves, and even hairs are also sources of tannin.

Previously, we pointed out the possible role of tannins in the induction or promotion of pemphigus.⁸ Some of the possible effects of tannins are listed below:

Precipitating interaction with proteins	Alveolar macrophage stimulation
Interaction with drugs	Platelet activation
Effect on nutrition	Enzyme inhibition
Release of neutrophil chemotactic factor	Metal ion deprivation

There is also evidence suggesting that tannins inhibit copper utilization.²¹ Interestingly, the well-known pemphigus inducer penicillamine is a chelating agent for copper. Polyphenols induce apoptosis.²² Tannins also induce binding of IgA paraprotein to red blood cells in a manner analogous to tanning (waterproofing and preserving animal skins to make leather) with phenolic plant extracts. Tannins react with structures on or in the red blood cell membrane.²³ Tannin is frequently used as a cross-linking agent,²⁴ and similar cross-linkage in the epidermis may possibly be the mechanism through which these compounds induce pemphigus. Similarly, the first step in drug-induced acantholysis involves binding of the drug to the cell membrane.

Tannic acid has often been used in electron microscopy as a stain for carbohydrate-rich cell surfaces. Tannic acid stains the cell surface and intercellular material in squamous epithelium and the desmosomes.²⁵ Tannins may activate platelets and are implicated in the epithelial injury of bronchi by cotton dust. Some are carcinogens, linked to nasal sinus cancer in woodworkers, squamous cell carcinoma of the oral mucosa, and gastrointestinal malignancies. Tannin has been shown to produce a cytotoxic effect on human peripheral blood lymphocytes in vitro, although this effect is dependent on increasing concentrations and time of exposure.²⁶

Other factors affecting tannin activity include the steric structure of both the tannin and the protein, absorption, and the composition and size of the protein on which the tannins act. Temperature, pH, and the presence of metal ions, calcium, and other chemical compounds will also influence tannin activity.

Intake of Tannins. Examples of Foods Containing Tannin. Cassava (*Manihot esculenta* Crantz), also known as manioc, mandioca, Brazilian arrowroot, and yucca, is an important dietary staple in many forms for more than 500 million people in South America, Africa, and Asia.²⁷ Cassava roots and leaves contain cyanogenic and noncyanogenic glycosides. Cassava leaves (both red and white varieties) also contain condensed tannins. The tannin content of oven-dried (70°C for 3 days in an air oven) cassava leaves is from 0.2 to 3 g/100 g, depending on the variety of cassava, and that of blanched leaves (100°C for 5 minutes) is 0.15 to 0.22 g/100 g.²⁸

Mango also contains high amounts of tannin in the pulp and skin, though this varies with the different kinds of mango. India is the largest producer of mango, with over 60 varieties grown there. The cashew tree produces apples (not a true fruit botanically) in addition to the nuts, and these apples are rich in tannins and are used to make juice and alcoholic drinks in Brazil.

The guarana plant is a perennial climbing shrub native to Brazil and other wooded Amazon regions. In recent years, products manufactured from guarana have been imported into the United States. The fruit is reddish and contains glossy brown seeds. Some Indian tribes grate fresh seed and swallow it with water, and some make a fermented drink. Sometimes it is dry roasted and then ground with cassava. This mixture of 2 high-tannin foods might have important implications. The greatest use of guarana presently is as a soft drink, which is imported to the United States. Guarana contains a high caffeine level as well as tannin. The total tannin content of air-dried guarana is 12.1% (proanthocyanidins and prototannins).²⁹ The seeds before any treatment contain 6% tannin.

Fruits such as the kola nut, betel nut, black walnut, raspberry, cherry, cranberry, and blackberry are all high in tannin content. Avocado, banana, apple, and pear are also rich in tannins, as are peach, persimmon, eggplant, and grape skins. Coffee and cocoa seeds and the roots of ginger, ginseng, and garlic are tannin rich, as are the leaves of cassava, tea, maté, and rosemary, the stems of vanillin, and the shells of carob. Provisions such as beer, wine, and soft drinks contain tannin additives. Tannin is also added to candy, ice cream, baked goods, and even nutritional supplements.

Stimulants and Masticatories. Certain plants that are used for recreational and social ingestion and also as aphrodisiacs and medications are rich in tannins (**Table 1**). To this category belong the guarana from Brazil, betel nut or areca nut (*Areca catechu*) from Malaya, which is popular in India and in many other countries in that region and in South Africa, and the kola nut from west Africa. The appeal of exotic products has led to their spread to North America as well, where they are now sold in sundries shops and grocery stores. Guarana and kola nut are also rich in caffeine and are used as stimulants.³⁰ Chewed

Table 1. Tannin and Caffeine Content of Some Masticatories and Stimulants*

Substance	Tannin Content	Caffeine Content
Guarana	12	3-5
Coffee beans	0.7	1-2
Roasted coffee beans	1.7	...
Dry tea leaves	3.7	1-4
Kola nuts (<i>Cola nitida</i> , <i>Cola acuminata</i> , family Sterculiaceae)	3.9-4.4	1.5-3.2
Maté	7-11	1.0-1.5
Betel nut (<i>Areca catechu</i> L)	8-15	Negligible
Betel leaf (<i>Piper betle</i>)	1.0-1.3	Negligible
Katha (derived from <i>catechu</i>)	11.7-14.2	Negligible
Cassava leaves	0.15-3.0	Negligible

*Tannin and caffeine contents are measured as a percentage of dry weight. Ellipses indicate not available.

betel nuts release tannins and thiocyanate. Immature nuts contain 38% to 47% tannin, mainly polymerized leukocyanidins, but the percentage decreases as the fruit matures, and processing reduces the level to 8% to 15%.

Betel nut addiction afflicts at least 10% of the human race.³⁰ The betel quid is a package of fresh betel leaf (*Piper betle* vine), the undersurface of which is smeared with lime, containing pieces of betel nut and tobacco. Spices are sometimes added too, as well as mustard. The leaves that are used for chewing contain 1% to 1.3% tannin and other phenols. The leaf yields 0.62% to 2.4% volatile oil, which is 75% phenolic.³⁰

The nut itself, aqueous extracts of it, and specific constituents in the nut can be mutagenic and carcinogenic.³¹ Several phenolics from the chewed plant products can generate free radicals that can exert a cytotoxic effect on the oral mucosa.³² It is a common practice to keep pieces of the nut or betel quid in the mouth for prolonged periods of time. Betel nut constitutes 50% of the betel quid by weight, and a person may consume the equivalent of 20 to 30 nuts and 200 leaves of betel vine per day.

One method of preservation of the fresh betel nuts involves blanching them in boiling calcium chloride. The calcium (lime) component of the betel quid may take part in pemphigus pathogenesis because the reaction of pemphigus autoantibodies is enhanced by calcium supplementation.

Another ingredient of the betel quid, katha, is derived from the heartwood of the cutch tree (*A catechu*), and contains 11.7% to 14.2% tannin. It is a potent tanning agent; 0.45 kg of cutch is equal to 3.2 kg to 3.6 kg of oak bark for tanning purposes. It is also used as an antioxidant in vegetable oils. An aqueous solution of *A catechu* bark containing catechin and tannin, prepared as a tincture or powder, has been used in the United States as an astringent coloring in liquors, soft drinks, ice cream, candy, and baked goods.

The expression of antigens that are markers of epithelial differentiation may be regulated by substances such as retinoic acid or calcium. Moreover, these antigens may be involved in cell-to-cell adhesion in the epidermis.³³ Thus, the same food compounds that play a role in car-

Table 2. Tannin and Calcium Content in Spices, and Average Daily Consumption per Individual in India

Spice	Tannin, g/100g	Calcium, g/100g	Spice Consumed, g/d*	Tannins Consumed in Each Spice, mg/d
Garlic (<i>Allium sativum</i>)	0.12	0.11	2.49 ± 2.78	3.0
Dry ginger (<i>Zingiber officinale</i>)	0.54	1.47	0.04 ± 1.31	0.2
Red chillies (<i>Capsicum annuum</i>)	0.90	0.06	3.08 ± 2.06	24.6
Asafoetida (<i>Ferula foetida</i>)	0.80	1.01	0.06 ± 0.10	0.5
Coriander (<i>Coriandrum sativum</i>)	0.82	0.65	1.37 ± 1.30	11.3
Cumin seeds (<i>Cuminum cyminum</i>)	0.90	0.92	0.80 ± 0.77	7.2
Black pepper (<i>Piper nigrum</i>)	0.94	0.38	0.33 ± 0.30	3.1
Ajowan (<i>Carum copticum</i>)	1.26	1.26	0.11 ± 0.17	1.4

*Values are expressed as mean ± SD.

cinogenesis of the mouth may play a role in cell-to-cell adhesion leading to the development of pemphigus. However, a combination of factors is needed: carcinogenicity has been shown to occur as a result of chewing a mixture of pepper leaf, betel, and lime but not the betel nut without lime.³⁰

Interestingly, chronic exposure to cashew nut oil has been shown to cause oral carcinoma in women who refrain from tobacco and betel nut habits.³⁴ In addition, oral submucous fibrosis, a precancerous condition, is prevalent among cashew workers in south India.³⁵ Chromosome breakage observed among betel nut chewers has been attributed to the joint action of betel nut-derived alkaloids, polyphenols and/or tannins, and nitrosamines in the saliva.

Kola nuts (*Cola nitida* and *Cola acuminata*, family Sterculiaceae) were carried to America from Africa with the slave trade in the 17th century³⁰ and spread due to the reputation of the seeds as stimulants. Tannin levels in *C nitida* are 3.9% to 4.4%, and total polyphenol levels are 6.7%, particularly catechol and epicatechol. Kola nuts are consumed fresh wherever they are grown throughout the world, and aqueous extracts or concentrates are used as flavorings in soft drinks, particularly with extracts of coca leaves.

Nuts such as peanuts and pistachios may contribute to pemphigus induction because people who eat them have a habit of sucking the shells. These shells have high tannin content.

Drinks. Tannin is the main component of tea,³⁶ and coffee also contains a substantial amount of tannin.³⁷ Maté, also called yerba maté, Brazilian tea, or Paraguay tea, is a tealike beverage popular in many South American countries. It is brewed from dried leaves of an evergreen tree, *Ilex paraguarensis*, and contains caffeine (1%-1.5%) and tannin (7%-11%). The plant grows wild in southern Brazil, where pemphigus is endemic in the Parana and Paraguay river basins.³⁸

Fruit juice, beer, wine, and liquor are all sources of tannin. Tannins are used in the clarification of wine and beer. Distilled liquor contains spices and flavoring agents such as vanillin and cinnamon that contain tannins. But the most intriguing issue is water. Possible constituents and effects of water have been discussed in detail in a previous publication.⁹ South American pemphigus foliaceus (endemic pemphigus, fogo selvagem) affects individuals of all ages and has a familial prevalence where it

is endemic in areas of Brazil. This has prompted a search for environmental factors.³³

Most patients with fogo selvagem live in close proximity to rivers. Many of these rivers contain high levels of tannin caused by decomposing leaves and other vegetable matter from the lush surrounding forests. Along these rivers, fogo selvagem occurs in regions where the weather is hot and humid. These conditions are needed for tannins to decompose, fitting our hypothesis that tannins in the water are an important factor in pemphigus.

The number of new cases of fogo selvagem is highest at the end of the rainy season and lowest during the dry summer. Rainfall causes a rise of the waters; large quantities of organic materials are then carried by the stream, and the amount of tannins dissolved in the water increases. Furthermore, variations of annual rainfall result in differences in the tannin content, and this may account for the observation that new fogo selvagem cases occur in clusters.³⁹

A possible lead toward a means for controlling pemphigus lies in the fact that chlorination of water results in the formation of the hypochlorite ion that combines with phenolic compounds even in high dilutions. This might account for the disappearance of fogo selvagem following urbanization, which usually involves treating of the water.

Spices. Spices have a high tannin content, ranging from 0.12 g/100 g to 1.26 g/100 g (**Table 2**). Spices of the Umbelliferae family (ajowan, coriander, and cumin) and black pepper have the highest content of tannin. All over India, where pemphigus is prevalent, spices constitute an important part of the daily diet.⁴⁰ Among spices, red chillies account for the highest daily tannin consumption by individuals in India, followed by coriander, cumin seeds, black pepper, and garlic. It is noteworthy that patients showing positive skin-prick test results to fresh fruits and vegetables also exhibited positive skin-prick reactions to spice (mustard included).⁴¹

Calcium ions are necessary for the reaction of tannins, tannins' action resulting in elevated intracellular calcium ion concentration. Interestingly, dry ginger, ajowan, and asafoetida, which are spices with high tannin content, also have high calcium levels.⁴¹

Food coloring. Several food coloring products have high tannin content. Mangosteen, a tropical fruit that originated in Southeast Asia, was introduced into the Americas centuries ago. Its skin contains 13% tannin and is used

as a coloring for food. The use of the catechu bark as food coloring was discussed earlier. It is also used as an antioxidant in vegetable oils.

Nutritional Supplements. Several popular nutritional supplements contain high concentrations of tannins. Some preparations are bark extracts containing proanthocyanidins and other polyphenols. There are also grape seed extracts containing flavonoids, tea extracts with high levels of tannins, and mixtures of extracts with high tannin levels.

CONCLUSIONS

In summary, inferences that diet plays a role in pemphigus induction may be drawn from a wide variety of facts: (1) The molecular structure of many food ingredients is similar to that of known pemphigus-inducing drugs. (2) Case reports^{6,7} indicate the connection. (3) Tannins and phenols are known to interact with proteins. (4) Seasonal variations in pemphigus incidence coincide with seasonal tannin variations in diet. (5) Yearly variations in pemphigus outbreaks coincide with yearly tannin variations. (6) Incidence of fogo selvagem drops as populations move into urban areas with chlorinated water supplies.

Finding the exogenous stressors is the first step toward their elimination. The second step is unfolding the sequence of events and the interaction between these stressors. The task is enormous and includes many variables, as even changes in the mode of preparation of the same foods might eliminate the deleterious effects of certain constituents.

We suggest that foods containing thiol, phenolic compounds, and polyphenols have a role in pemphigus. But which of the multitude of these compounds are involved, their mode of action, and under what conditions their effect is exerted still remains to be unveiled.

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