

American Herbal Pharmacopoeia®

White Mulberry (*Morus alba* L.) Leaf Use and Safety Assessment of Adverse Effect Report Reporting of Event & Dietary Supplement Regulation



Compiler

Roy Upton RH DipAyu
President, American Herbal
Pharmacopoeia®

Thomas Avery Garran PhD
Herb Whisperer, LLC
Beijing, China

Debbie Shaw PhD
National Poisons Information
Service
London, United Kingdom

Technical Review

Eric Brand PhD, LAc
Taipei Medical University
Taipei, Taiwan

Bill Gurley PhD
Principal Scientist
National Center for Natural Product
Research
University of Mississippi
Oxford, MS

Elan Sudberg BA
Alkemist Labs
Garden Grove, CA

John Chen PhD, PharmD, OMD, LAc
President, Editor
Art of Medicine Press
City of Industry, CA

Christine Leon PhD
Royal Botanic Gardens-Kew London,
United Kingdom

Legislative Review

Holly Bayne JD
Bayne & Associates
Washington, DC

Stefan Gafner PhD
American Botanical Council
Austin, TX

Professor Dr Judith Rollinger
University of Vienna
Vienna, Austria

Communications

Roy Upton
831-461-6317
831-247-4607
herbal@got.net





American Herbal Pharmacopoeia®

WHITE MULBERRY (*Morus alba* L.) LEAF USE AND SAFETY ASSESSMENT OF ADVERSE EFFECT REPORT REPORTING OF EVENT & DIETARY SUPPLEMENT REGULATION

EXECUTIVE SUMMARY

BACKGROUND

- On August 24, 2022, *Kaiser Health News* reported on the passing of a 61-year old California woman who died from dehydration in December of 2021.
- The Kaiser article was based on a Certificate of Death and Coroner's Report alleging cause of death as "dehydration due to gastroenteritis due to adverse effects of white mulberry leaf ingestion."
- Autopsy revealed a partial fragment of a leaf in the stomach contents of the decedent that was putatively identified as white mulberry (*Morus alba*).
- No information was provided as to how cause of death was attributed to the leaf fragment, there was no indication a dietary supplement product was ingested, and botany experts informed the Coroner's office "White mulberry is not toxic"
- The Kaiser article used the incident to suggest that because supplements are not regulated in the same way as pharmaceuticals that they are potentially dangerous though provided no evidence that a supplement was ingested.
- Mulberry leaf has been used as a food, animal fodder, health supplement, and medicine in Asia for at least 1,800 years.
- Formal clinical trials and toxicological investigations of mulberry leaf and its extracts demonstrate a high degree of safety in humans and animals even at high doses.
- A review of mulberry's pharmacological activity provides no indication that it possesses any activity that would suggest it would be either causative or contributed to this event.

CLINICAL TRIALS

- Clinical trials demonstrate the safety of white mulberry leaf extract when used at doses of up to 4.6 g (the leaf fragment was estimated at 167 mg).
- Some clinical trials report mild digestive upset as an adverse effect with others demonstrating greater digestive upset in placebo groups.



- White mulberry and its extracts reported as well tolerated in all studies.
- No serious adverse effects from white mulberry leaf were reported in a meta-analysis of 13 studies involving 436 participants.

FORMAL TOXICOLOGICAL EVALUATIONS

- In humans, doses of white mulberry leaf extract of 3,000 and 3,600 mg daily are reported as safe and well-tolerated.
- In animals, mulberry leaf fed in kilogram amounts, even in pregnancy, reveal no evidence of toxicity.
- In pre-clinical toxicity studies in varying animal models, no acute, chronic, or genotoxic effects, and no negative changes in hematological, biochemical, or histopathological parameters were reported at doses up to 15 g/kg.
- Toxicology experts confirm that available data suggests a lack of toxicity associated with white mulberry leaf and likely not the cause of the event.
- Formal toxicological and safety reviews suggest white mulberry and its extracts are safe.
- A review of pharmacovigilance data internationally reveals few reports of adverse effects.

ASSESSMENT OF REPORT OF FATALITY

- Gastroenteritis was reported as the cause of death but the autopsy revealed tissues of the gastrointestinal system were normal.
- No information was given as to why mulberry leaf was considered causative or contributory to the event.
- There is no indication that any nationally or internationally accepted process for determining causality was conducted.
- Other common causes for gastroenteritis or dehydration, such as bacterial or viral infection, effects of dieting, or the potential for digestive disorders due to COVID vaccination, were not ruled out.
- The decedent experienced stomach upset the day before passing. Stomach contents empty within 1.5 to two hours presenting the possibility that something else may have triggered the event but was no longer observable in stomach contents.



BOTANICAL IDENTIFICATION OF LEAF FRAGMENT

- Botanical experts putatively identified the leaf fragment as fresh white mulberry and reported to the coroner that white mulberry is not toxic.
- Fresh mulberry leaf is generally not available commercially but does occur in gardens.
- Botanical authorities question the ability to determine with definitiveness the identity of a small leaf fragment that has been exposed to the gastric environment.
- Other leaves, including those within the highly toxic *Aristolochia* genus used as ornamental plants, possess the same physical characters as mulberry species.
- Key identifying characteristics of white mulberry were not assessed.
- Fresh leaf the size of the fragment found is difficult to swallow without initiating a gag reflex. The fragment would likely have to be swallowed within a bolus of food or soup; however, the coroner reported there were no other contents present in the stomach.

MEDIA REPORTING OF EVENT—FATALITY CAUSED BY A “HERBAL REMEDY” OR “DIETARY SUPPLEMENT”

- A substantial amount of the reporting on this event focused on the potential risks and regulations of herbal and dietary supplements though no indication that any supplement was taken was presented.
- Suggests safety of supplements can be improved by more rigorous regulations such as those applied to pharmaceuticals but fails to acknowledge that adverse events due to supplements are rare while pharmaceuticals are among the most common cause of deaths internationally and pharmaceutical manufacturers have been subject to numerous violations that include non-conformity with good manufacturing practices and fraud resulting in hundreds of thousands of deaths annually (e.g., opioid crisis)
- Misrepresents the science on white mulberry stating that mulberry leaves “do tend to cause dehydration...” There is no evidence in the historical, clinical, or pharmacovigilance data to support this statement.
- A primary driver of supplement use in the US is a desire to be healthy, to take active steps in maintaining and improving health, to minimize the need for potentially harmful synthetic medications, and to fulfill health care needs not adequately addressed in conventional care. This should be encouraged not dissuaded.

CONCLUSION

- AHP has a history of reviewing the traditional and modern literature on botanical ingredients used in supplements and medicines and subjecting its work to a multi-disciplinary review of medicinal plant experts worldwide. The accompanying review



American Herbal Pharmacopoeia®

addresses the assertions made regarding the putative toxicity of white mulberry and the manner in which the information was presented.

- There is no evidence in either the traditional or modern literature to suggest that white mulberry leaf exhibits a toxic potential to have caused or contributed to this event.
- A review of the world's pharmacovigilance data gives no indication of any toxic potential regarding white mulberry leaf.
- There is no indication that the Coroner's office followed any formal mechanism for assigning causality.
- Independent botanical experts indicate that a definitive identity of a small leaf fragment soaked in stomach fluids cannot be made.
- Experts in Chinese herbal medicine, conventional medicine, integrative medicine, pharmacology, and toxicology concur that there is nothing in the available autopsy reports or historical or scientific literature that could suggest white mulberry leaf was either causative or contributory to this event.

Epilogue

- Three weeks after the initial Kaiser article, writer Samantha Young released a follow-up similarly questioning how causality was determined.
- Cites medical, pathology, and pharmacology experts who concur that mulberry is non-toxic, that causation could not be determined based on the available information, and that one partially digested leaf would "not have contributed to death."

PERSONAL NOTE OF CONDOLENCES

Because of AHP's network of experts in botanical medicine, we sometimes have to work on issues we would prefer not to. It is with great regret that we have to write anything about the passing of a person whom we did not know. We offer our sincerest condolences to the family and friends of the deceased and our heartfelt apologies for having to address this issue at all.

WHITE MULBERRY (*Morus alba* L.) LEAF USE AND SAFETY ASSESSMENT OF ADVERSE EFFECT REPORT REPORTING OF EVENT & DIETARY SUPPLEMENT REGULATION

Full Report

BACKGROUND AND SUMMARY

On August 24, 2022, *Kaiser Health News* (KHN) reported on the passing of a 61-year old California woman who died from dehydration in December of 2021 (Young 2022a). According to KHN, the death was caused by severe stomach inflammation from consuming an “herbal remedy” or “dietary supplement” containing white mulberry leaf (*Morus alba*). The article was based on a Certificate of Death and Coroner’s Report issued by the Sacramento County Coroner’s office alleging that the cause of death was “dehydration due to gastroenteritis due to adverse effects of white mulberry leaf ingestion.” An autopsy was performed and a partial fragment of a leaf was found in the stomach of the victim (Fearne and Tovar 2021; Rogers et al. 2022). The leaf was subsequently putatively identified as white mulberry (*Morus alba* L.) (Colwell et al. 2021), a common Chinese herb primarily used for supporting healthy respiration and relieving coughs. Additionally, based on traditional use and modern controlled clinical studies various white mulberry leaf preparations have been found beneficial for supporting healthy blood sugar levels and healthy weight management (Gheldof et al. 2022; Liu et al. 2016; Lown et al. 2017; Jeong et al. 2022, among others). The decedent reportedly was dieting.

No information was provided in the article or coroner’s report as to how the cause of death was attributed to the leaf fragment and there was no indication that any dietary supplement product was ingested. A follow-up article by the same writer Samantha Young released three weeks after the original, similarly raised questions regarding how mulberry leaf was considered causative and cited numerous experts, including in



pathology, who generally acknowledged that mulberry leaf is considered non-toxic (Young 2022b).

In contrast, the report of botanical identity issued by botanists at the University of California-Davis, informed the coroner's office that "the leaf was likely ingested when fresh" and that "White mulberry is not toxic" (Colwell et al. 2021). It is not known why the coroner disregarded the opinion of expert botanists. It is also not known how the assumption was made that a dietary supplement had been ingested as suggested. Fresh leaves are not typical ingredients in finished dietary supplements, but rather are consumed as foods or eaten while foraging.

In addition to reporting on the fatality itself, a significant portion of the KHN article was devoted to suggesting that because herbal and nutritional supplements are regulated as "food" they do not "undergo the rigorous scientific and safety testing the government requires of prescription drugs and over-the-counter medicines." However, the article itself rightly states there is no indication a supplement product was actually ingested, but does go on to suggest greater regulatory requirements are needed.

Commentary such as this underscores the lack of familiarity within the conventional medical world regarding food and supplement regulations. Federal regulations require that foods and supplements be safe for their intended use or the Food and Drug Administration (FDA) may remove them from the market. Worldwide, there is a relative lack of adverse effects of supplements despite their widespread use. This is in stark contrast to significant dangers of approved pharmaceuticals, the product category to which supplements was compared. This narrative regarding supplements similarly ignores the fact that blueberries, garlic, coffee, scrambled eggs, peppermint leaves, green tea leaves, and a host of other commonly consumed foods and botanicals have similarly not been subjected to the same regulatory requirements needed for proving the safety and efficacy of pharmaceuticals. Yet, tens of millions continue to consume these common ingredients on a daily basis, and specifically regarding supplements, express a high degree of satisfaction from their use, an opinion that has been maintained for decades (Devitt 2001; Hunt 2001).



The vast majority of foods and herbs have remained in the public domain for centuries precisely because of their high degree of safety and acknowledged value in human health and nutrition. The World Health Organization (WHO) and many regulatory bodies worldwide, recognize the immense contribution that botanical and nutritional products make to human health. In the United States (US) it is completely opposite. Conventional health practitioners and regulatory agencies here often consider there to be no benefit to supplements, strongly discourage self-care, and believe the modalities they provide have been proven “safe and effective”. What they fail to recognize is that the US provides very little “health care” and predominantly focused on “disease care”. The medical literature is replete with examples of how badly the medical system in this country is broken and they do not know how to fix it. Americans spend more on medical care than anyone else in the world and have among the worst health care statistics for it (see Chemweno 2021; National Academies 2013; Weil 2013, Woolf and Aron 2013; among others). The US is unique in the world in not having a mechanism by which traditional herbal medicines are recognized so their benefits can be made known to consumers. Because of this, consumers take it upon themselves to take active measures to improve their health. The use of supplements is integral to this and should be encouraged not disparaged.

Specifically, mulberry leaf has approximately 1,800 years of accumulated information regarding its safety when used as a food, health supplement, and traditional herbal medicine. Mulberry leaf has similarly been subjected to formal clinical and toxicological studies, as well as expert safety reviews, that confirm its safety (see Clinical Studies below). Clinical studies suggest it is good for blood sugar regulation and weight loss. With diabetes and obesity being among the leading causes of morbidity and mortality in the US, one would think the medical community and consumers would want to know about it.

Not mentioned in any of the media coverage of this event is that the supplement industry is highly regulated and subject to county, state, and federal laws that specifically ensure the safety and quality of supplement products. To suggest that broccoli, chamomile tea, echinacea, garlic capsules, and mulberry leaf should be



regulated in the same way as powerfully acting synthetic medications and artificial hearts is to ignore that humans have been using these as an integral part of self-health care, in some cases, for multiple generations.

The American Herbal Pharmacopoeia (AHP) has a history of reviewing the traditional and modern literature on botanical ingredients used in supplements and medicines and subjecting its work to a multi-disciplinary review of medicinal plant experts worldwide. Each AHP review includes experts in botany, herbal medicine, chemistry, pharmacology, pharmacy, medicine, toxicology, and specialists in traditional Ayurvedic, Chinese, and Western herbal medicine.

Based on a review of the historical and scientific literature, of which both are extensive, there are no documented reports of mulberry leaf toxicity and mulberry leaf appears to lack any significant known pharmacological action that would either cause or contribute to such an unfortunate event.

Following is AHP's assessment based on the information currently available. Further assessment may be possible if more information regarding this case emerges. AHP will continue to monitor this case for any new information that may become available.

SCOPE

Due to the scarcity of data regarding this event, the focus of this assessment is on the identity of white mulberry, a review of its historical use as a food, health supplement, and medicine, its general safety, and a brief overview of clinical and toxicological research. Reviewers of this assessment were chosen for their expertise in botany, traditional Chinese herbal medicine, medicine, pharmacology, pharmacognosy, and toxicology. Each reviewer was provided the Coroner's and botanical identification reports. Additional comments are provided regarding the manner in which information relating to this case was disseminated as considerable misrepresentations and some inaccuracies were made in various media.



ASSESSMENT LIMITATIONS

- This assessment is limited to the information available at the time of its writing (September 9, 2022).
- No independent authoritative analysis of the coroner's report was conducted.
- Examination of the leaf fragment was not possible.
- Only a basic review of the pharmacology was done to help determine if there was any mechanistic plausibility for white mulberry leaf to cause or contribute to such an event.
- Public reports stated that the Coroner's office was not providing further comments regarding this case and so the office was not contacted.
- Out of respect for the tragedy of the event, no attempt was made to contact the family of the deceased for additional information.

WHITE MULBERRY LEAF (*Morus alba* L.) 桑叶

INTRODUCTION

White mulberry leaf consists of the dried leaf of *Morus alba* L. Traditional Chinese medicine (TCM) literature suggests that the ideal time to collect leaves is after the first frost when two-thirds of the leaves have fallen; the remaining one-third of leaves should be gathered (Li 1596). When picked in the autumn, the leaves are mostly yellowed to light green. If picked in the summer, leaves are darker green.

Form: Occurs either as whole leaves crumpled together or cut into smaller sections as decocting pieces (see Figures 5-6).

Processing and Methods of Preparation

Generally used in unprepared form either as whole or cut pieces (decocting pieces), though it is sometimes fried and processed with honey.

HISTORICAL ETHNOBOTANICAL AND CONTEMPORARY USE

All parts of the mulberry tree have historically been used, and continue to be used, primarily in Asia. The earliest recorded mention of white mulberry leaf occurs in the *Shennong Bencao*, the earliest materia medica of China. The original herbal is estimated to have originated around the 3rd century. The most definitive English translation of the *Shennong Bencao* primarily focuses on the use of the root bark, gives brief mention of the leaf, and there is no mention of mulberry leaf toxicity (Wilms 2017). A later 5th century compilation of the same text classifies mulberry as “slightly toxic” but there appears to be no other record in materia medica literature that repeats this. Tao Hong Jing refers primarily to the use of the root, recording that the part of the root that is growing above ground is toxic but similarly gives no mention of any toxicity of the leaf (Wilms, Garran 2022; personal communication to AHP, unreferenced).

The most comprehensive compilation of herbal medicine knowledge after the *Shennong Bencao* was the *Bencao Gangmu* compiled by Ming Dynasty physician Li Shizhen (1596) who cited more than 700 references, recording the herbal knowledge of

the most authoritative materia medica writers before him. Li gives extensive discussion of white mulberry leaf, acknowledges the earlier report of Tao Hong Jing, and cites numerous other authorities, all of whom attest to the leaf's safety as a food, health supplement, and medicine, providing a record of several hundred years of safe human use (Li 1596).

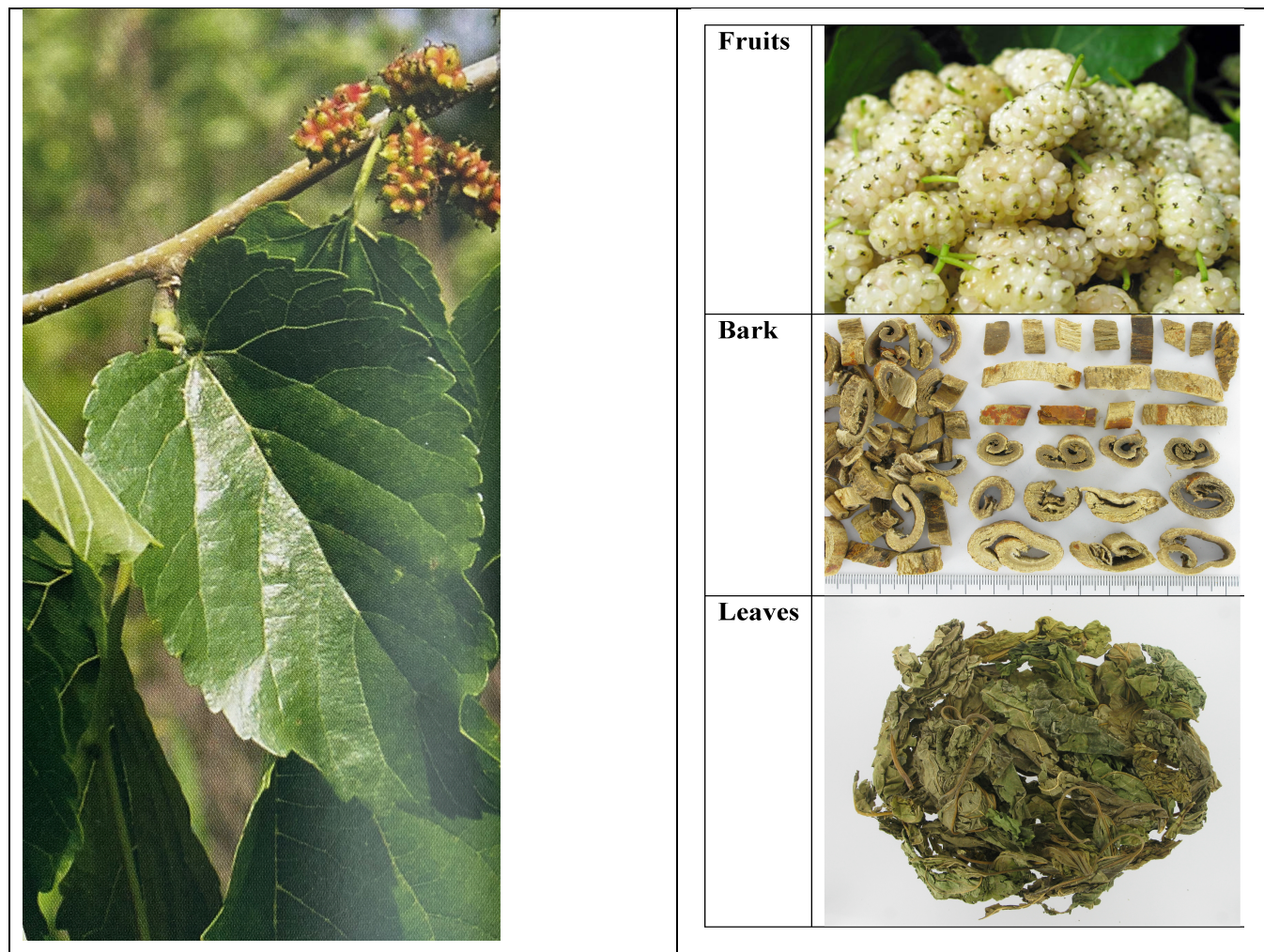


Figure 1 White mulberry and its plant parts used in food, health supplements, and medicines

Source: Leon C, Lin YL. 2017. *Chinese Medicinal Plants, Herbal Drugs and Substitutes: An Identification Guide*. London. Kew Publishing, Royal Botanic Gardens, Kew. 806.

Use of Mulberry Leaf as Food

Historically, white mulberry leaf was considered safe for long-term use to promote health. Li Shizhen (1596) cites earlier authority Su Song who reported:



“Sangye [white mulberry leaf] can be used regularly over a long time. Hereunder it is a prescription of life prolongation...This is called mulberry leaf for the immortals.”

In the same text (Li 1596) it is recorded that a decoction of fresh mulberry leaves is used to treat the vomiting, diarrhea, and abdominal pain associated with cholera, suggesting a historical use of benefitting the intestines. Since that time, white mulberry leaf has continued to be consumed as a food ingredient in China, Japan, and Korea (Zhang et al. 2022). Powder is used as an ingredient in cookies, yogurt, fruit preparations, and ice cream (Sujathamma et al. 2013), while the young leaves are harvested fresh, chopped into small pieces, and sautéed or steamed with other vegetables (Baronov 1966; Bastri 1962). White mulberry leaf is also officially recognized as a conventional food and health food in China (Leon and Lin 2017; MOH 2002). Professor Hu Shiu-Ying of Harvard University’s Arnold Arboretum reported that mulberry leaf was used in the fermentation of black soybean, and that roasted leaves are drunk as a common tea in certain regions of China (Hu 2005). In Greek cuisine, mulberry leaves are used as a vegetable (Baronov 1966; Bastri 1962); and in preparation of the Greek food dolma (Pieroni 2020).

The fresh leaves are used as fodder for cattle, poultry, goats, and sheep in India, China, Afghanistan, Latin America, and Central and East Africa, with no reported adverse effects on growth, performance, quality of products, and select hematological parameters in which kilogram amounts are fed to animals (see Hassan et al. 2020; Kandylis et al. 2009; Sujathamma et al. 2013; among others). White mulberry leaves have been a primary food of silkworms for at least four thousand years. The American Society for the Prevention of Cruelty to Animals report mulberry to be non-toxic to dogs, cats, and horses (ASPCA) 2022).

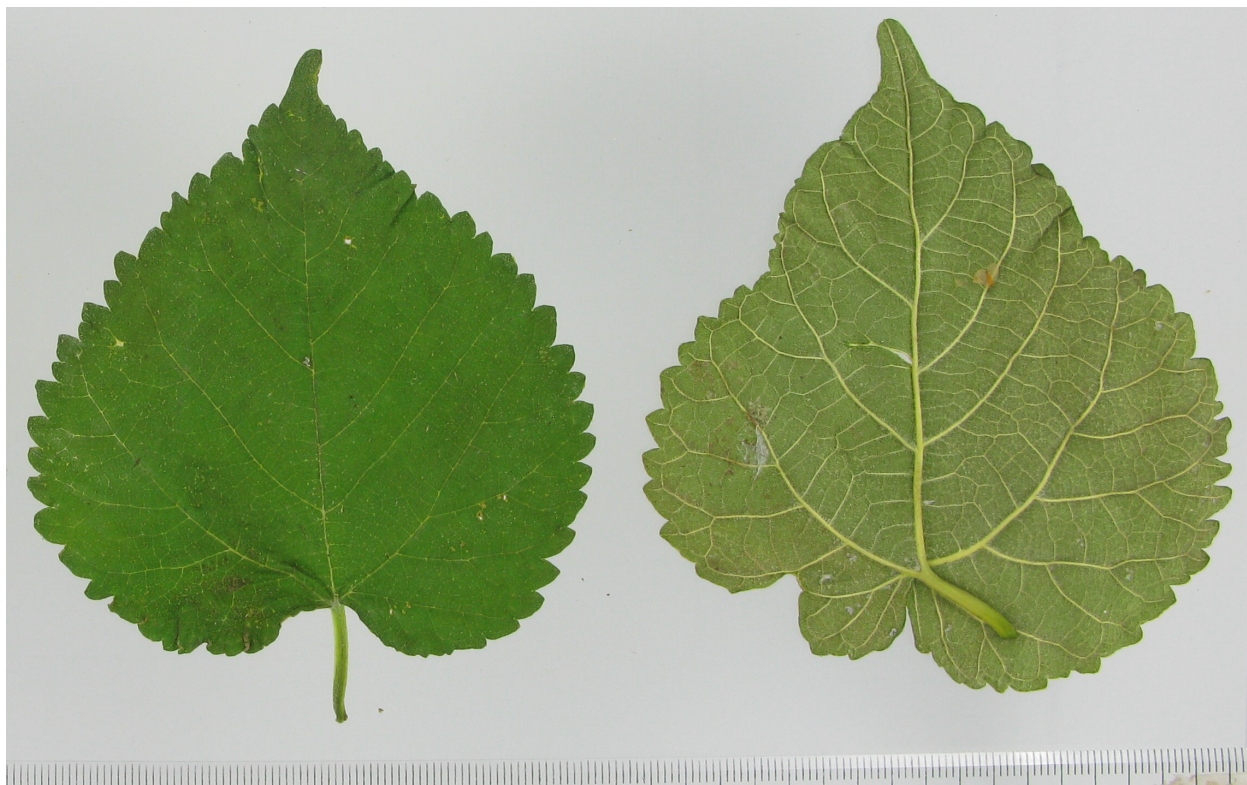


Figure 2 Fresh mulberry leaves

Use in Traditional Chinese Medicine

White mulberry leaf is a common ingredient used in traditional Chinese medicine, in which the standard daily dose is 4.5 to 9 g, typically consumed as teas or in formulas. There are no cautions recorded in the primary English-language Chinese materia medicas (Bensky et al. 2004; Brand and Wiseman 2008; Chen and Chen 2004) and similarly none recorded in the *Pharmacopoeia of the People's Republic of China* (PPRC 2015).

Mulberry leaf is a primary ingredient in herbal formulas widely consumed in contemporary times in China, most notably in *Sang Ju Yin* (*White Mulberry and Chrysanthemum Drink*). *Sang Ju Yin* is commonly used as part of a SARS prevention formula and is formally used in hospitals in China to protect health care workers, and has been since the SARS outbreak in 2002 (Lau et al. 2005). Though formal tonnage data are not available, this particular formula has been copiously consumed since the initial outbreak of SARS, and has continued to be used throughout the COVID-19



pandemic with no apparent pharmacovigilance signaling of a potential for adverse effects.

According to Dr. Thomas Avery Garran, herbalist, PhD (Chinese herbal pharmacy) and formerly of the China Academy of Chinese Medical Sciences, National Center for Materia Medica Resources in Beijing;

“I have looked at the Chinese literature regarding mulberry leaf fairly thoroughly, spanning nearly 1,800 years, and I have yet to find any caution regarding its use. Last year I gave my mother-in-law, whom I love, about eight pounds of it for a chronic cough she has due to pulmonary fibrosis and she has been drinking it almost every day for months with no untoward effects. When I first read the reports that mulberry leaf was responsible for someone’s death, I was shocked but also sure that determination was made by those unfamiliar with the botanical.”

IDENTIFICATION

Macroscopic Identification

Botanical Nomenclature:	<i>Morus alba</i> L.
Botanical Family:	<i>Moraceae</i>
Pharmacopoeial Nomenclature:	<i>Folium mori</i>
Standard Common Name:	White mulberry
Pinyin Name:	Sang ye (桑叶)
Part Used:	Leaf



Figure 3 White mulberry

Source: iNaturalist https://www.inaturalist.org/guide_taxa/882846

Macro-Morphological Leaf Characters

Blade:	Ovate or broadly ovate, 8-15 cm in length, 7-13 cm in width.
Apex:	Acuminate to acute or blunt.
Base:	Truncate, round, or cordate.
Margin:	Dentate, obtuse-dentate, or serrate, to shallow crenate.
Petiole:	Generally removed, 1.5-5.5 cm in length when present.
Upper surface:	Yellowish-green to light yellowish-brown, glabrous, sometimes with small warty protrusions.
Lower surface:	Lighter in color, yellowish, pinnate venation including bronchiododromous loop, prominent, lateral veins reticulate,



midvein sparsely pubescent; white tufts of trichomes occurring in the axils of the midvein and primary lateral veins.

Sensory Characteristics

Taste: Weak, slightly bitter and astringent.
Aroma: Slight.
Texture: Brittle; easily breaks apart when handled.
Fracture: N/A

Quality Characteristics

Good quality material consists of relatively whole large yellowish-green leaves without petioles.

Potential Adulterants

Commercial material is mostly cultivated. Adulterating species have not been reported.

References consulted: Bensky et al. 2004; HKBU 2022; KHP 2002; Leon and Lin 2017; PPRC 2015; THP 2019; Wagner et al. 2011.

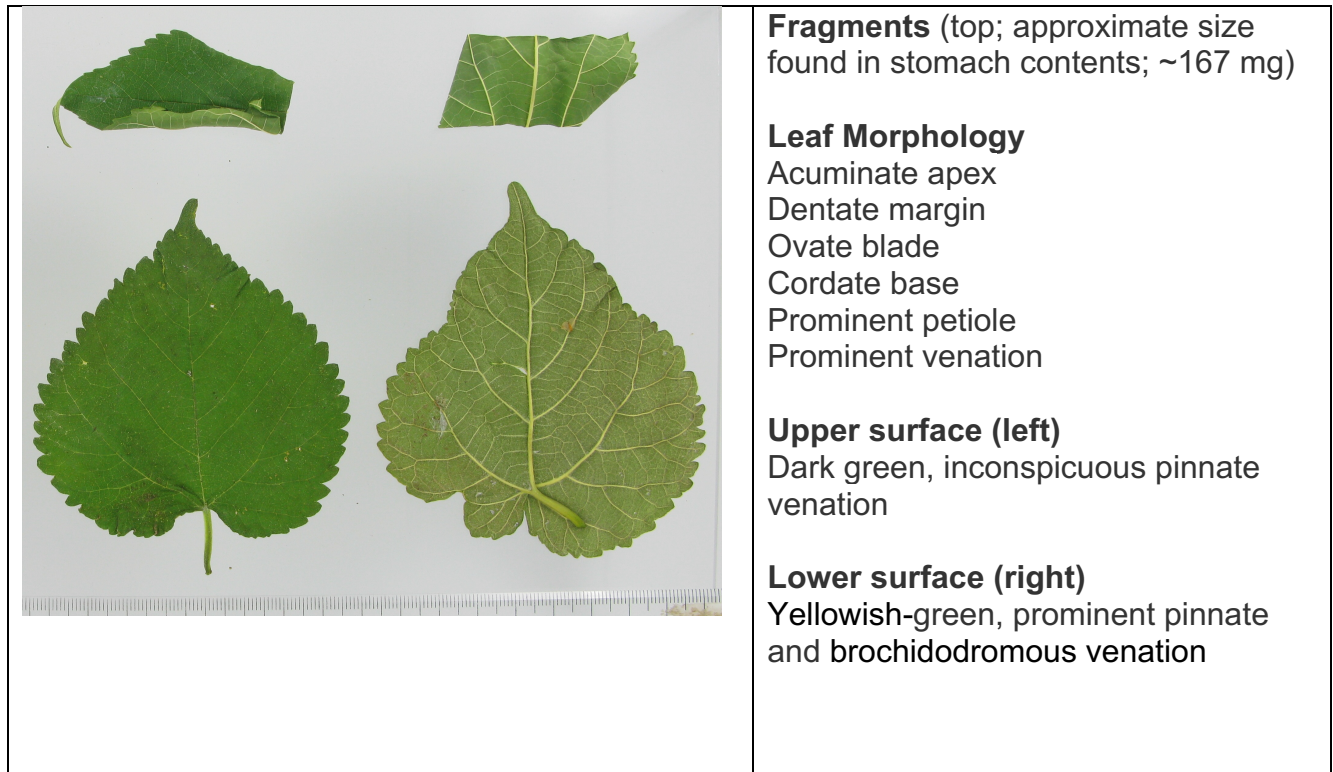


Figure 4 Fresh mulberry leaf picked prior to autumn yellowing and fragments approximating the size of the fragment investigated

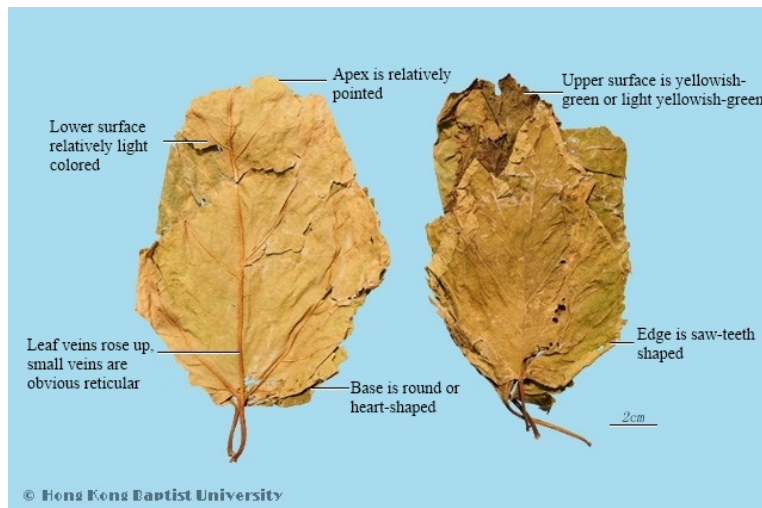


Figure 5 Dry white mulberry leaf picked in autumn
Source: HKBU Chinese Medicinal Material Images Database



Figure 6 Decocting pieces of fragmented dried white mulberry leaf (sang ye 桑叶) harvested after autumn yellowing.
1. Wart-like protuberances; 2. Prominent cream-color venation on lower leaf surface.
Source: Leon and Lin 2017.



Figure 7 Commercial Chinese sample of dry white mulberry dried leaf picked prior to autumn yellowing

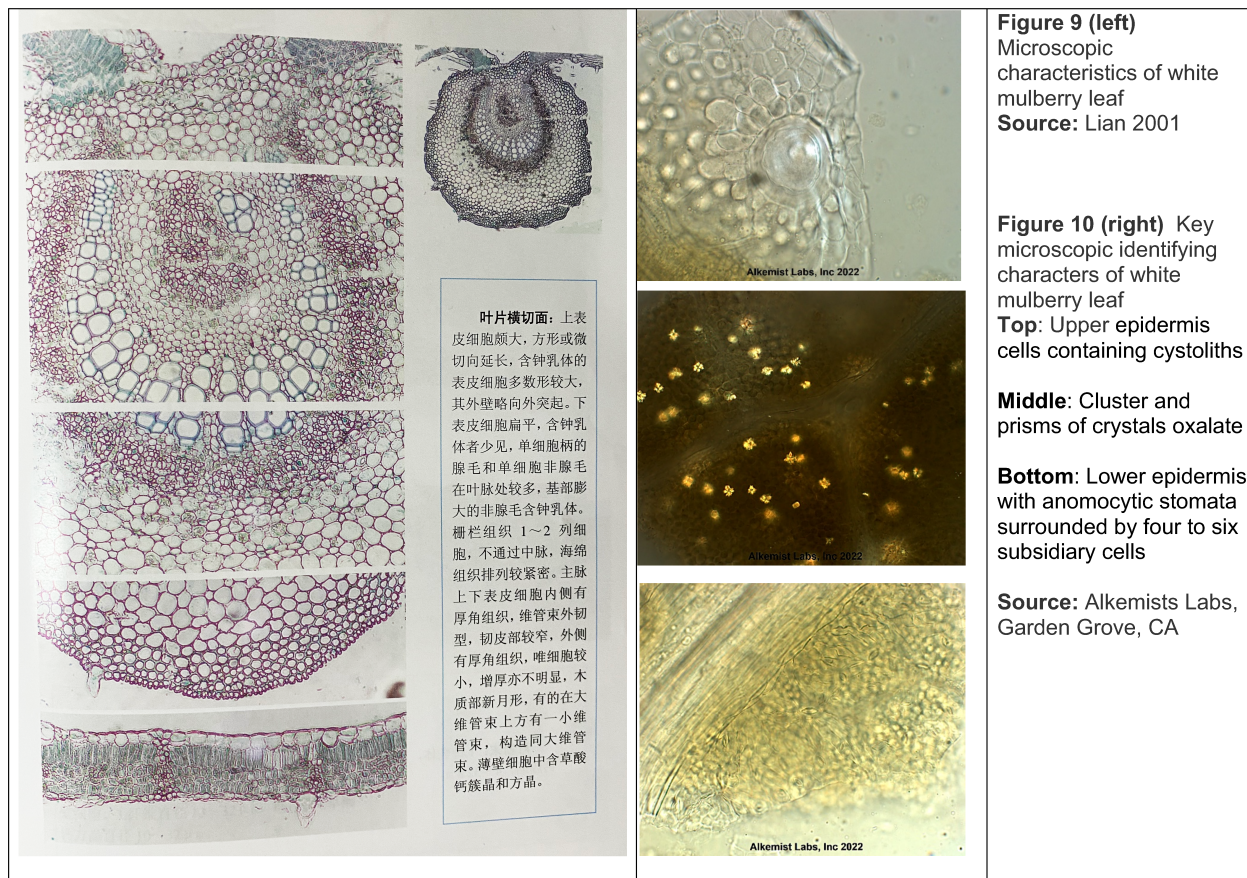


Figure 8 Lower surface of fresh white mulberry leaf showing characteristic white tufts of trichomes.

Source: Leon and Lin 2017.

Microscopic Identification

Transverse section: Upper epidermis with a single row of cells covered with a cuticular layer; cells are large, polygonal 15-30 μm in diameter with cystoliths and the outer wall slightly protruding. Unicellular glandular and non-glandular trichomes are present. Lower epidermis with a single row of flat, relatively small cells with numerous stomata. The main vein protuberant downwards, containing collateral vascular bundles; collenchymatous tissue scattered in the outer part of vascular bundles, cells relatively small, phloem narrow, xylem crescent-shaped, spiral vessels present (5-12 μm in diameter). Parenchymatous cells filled with abundant prisms and clusters of calcium oxalate. Palisade tissue 1-2 rows arranged densely, cells are square or subrounded 25-35 μm long and 2-6 μm wide. Spongy tissue with subrounded or polygonal cells 5-10 μm in diameter (THP 2015). For more detailed microscopic characterization of white mulberry see Klimko 2016.



CONSTITUENTS

White mulberry leaves contain a broad spectrum of constituents that are common to many plants, along with some that are common and relatively unique to the *Moraceae* [mulberry] family. The leaves are rich in carbohydrates and protein, as well as many vitamins and minerals such as beta-carotene, iron, calcium, and zinc (Srivastava et al. 2006), as well as constituents common to most plants (e.g., stilbenoids; resveratrol and oxyresveratrol), flavonoids (including quercetin and kaempferol), and anthocyanins (Kim et al. 1999; Song et al. 2009). Additionally, the leaves contain polyhydroxylated alkaloids that belong to a class of compounds known as iminosugars or azasugars and are among the characteristic identifying compounds found in *Morus* spp.

Nutritional Components

Fixed oil, lipids (2.09%-7.92%), carbohydrate (9.70%-39.70%), protein (15.31%-30.91%) including the amino acids valine, glutamine, leucine, glycine, lysine; dietary



American Herbal Pharmacopoeia®

fiber (9.9%-36.66%), fats (2.09%-7.92%). Vitamins beta carotene (8.44-13.13 mg/100 g), B, C (100-200 mg/g), D, calcium (786.66-2726.66 mg/100 g), magnesium (720 mg/100 g), potassium, phosphorus (970 mg/100 g), iron (19.00-50.00 mg/100 g), zinc (0.72-3.65 mg/100 g) (Butt et al. 2008; Ma 2022; Shahana et al. 2019).

Flavonoids

Mulberry contains many of the same basic flavonoids that occur in many plants including: epicatechin (20%), kaempferol (6%) and kaempferol derivatives (e.g., kaempferide 3-*O*-glucoside, astragalin [kaempferol-3-*O*-glucoside (26-36 g/100 g)], 7, 2', 4'- trihydroxyflavanone, luteolin (12%), apigenin, myricetin (10%), pelargonidin, quercetin (12%), rutin (457-659 mg/100 g), and numerous other quercetin derivatives (e.g., quercetin 3-*O*-(6-*O*-malonyl)glucoside, isoquercitrin [160-220 mg/100 g], quercetin-3-*O*-glucoside), and flavanes.

In addition to common flavonoids, mulberry leaf contains relatively unique compounds not as widely represented in higher plants including: 2-arylbenzofuran derivatives (moracins C, M, N, P, V-Y, chalcomoracin; albafulan A, wittifuran E, 2-(3,5-dihydroxyphenyl)-5, 6-dihydroxybenzofuran, morachalcones A-E (Chan et al. 2016; Deepa et al. 2013; Wen et al. 2020), norartocarpetin. Prenylated flavonoids include 3',8-diprenyl-4',5,7-trihydroxyflavone, kuwanon C, kuwanon G, kuwanon S (mulberrin) (Aelenei et al 2019; Butt et al. 2008; Dat et al. 2010), 8-geranylapigenin, cyclomulberrin, sanggenon J and K, cyclomorusin, morusin, atalantoflavone (Chan et al. 2016; Ma et al. 2022).

Non-Flavonoid Phenolics

Gallic, caffeic, proto-catechuic, vanillic, chlorogenic, *p*-coumaric, and ferulic acids; piceatannol, stilbenes (e.g., oxyresveratrol), coumarins (e.g. skimmnin, scopolin), tannin (0.13%-0.3%), and eugenol glucoside.



Terpenoids and Sterols

β -Sitosterol, β -sitosterolglycoside, ecdysteroids (e.g., 20-hydroxyecdysone and inokosterone) (Lafont and Dinan 2013), campesterol (Tang and Eisenbrand 1992).

Terpenoids include lupeol and saponins

Other Constituents

Polysaccharides, megastigmane derivatives (e.g., roseoside, syn. roseoside II), iminosugars (e.g., 1-deoxynojirimycin [DNJ] 0.15%-1.46%), loliolide, benzyl glucoside, alkaloids (D-fagomine and 3-epi-fagomine), volatile compounds and organic acids (citric, malic, tartaric, oxalic [183 mg/100 g]), (Chan et al. 2016; Doi et al. 2001; Kim et al. 1999, Ma et al. 2022; Mohammadi and Naik 2012; Shahana et al. 2019).

WHITE MULBERRY LEAF CONTEMPORARY RESEARCH

Subsequent to the KHN report, AHP conducted a literature review of the use of white mulberry leaf that included its historical and current use, clinical trials, toxicological evaluations, safety reviews, pharmacological activity, and national and international pharmacovigilance data. Additionally, the opinion of experts in toxicology, pharmacology, medicine, and traditional Chinese medicine were solicited. Based on this review, there is no indication that white mulberry leaf possesses any activity that could plausibly be considered to be causative or contributory to this unfortunate death, and, in contrast, possesses a high degree of safety even when used in high doses.

Clinical Studies

Formal clinical studies generally establish the safe use of a mulberry leaf extract for potential benefit in weight loss, blood sugar regulation, and metabolic syndrome. Doses up to an equivalence of 4.6 g of mulberry leaf are used. This is similar to the traditional dose used medicinally and is typically reported as well tolerated. The primary white mulberry extract used clinically has been subject to at least 10 clinical studies.

Pharmacological activity established in clinical trials demonstrate that white mulberry leaf significantly lowers fasting blood glucose (Andallu and Suryakantham

2001), slows the absorption of carbohydrates (Mudra and Ercan-Fang 2007; Zhong et al. 2006), and increases insulin sensitivity, thus its use in diabetes and supporting healthy blood sugar levels. Increased insulin sensitivity appears to be at least in part due to up-regulation of peroxisome proliferator-activated receptors (PPARs) (Park and Lee 2005), a group of nuclear receptor proteins that promote ligand-dependent transcription of target genes that regulate energy production, lipid metabolism, and inflammation. The roles of PPARs in metabolic regulation and carbohydrate and lipid metabolism are well established. In recent years, modulation of PPARs for supporting normal homeostasis of intestinal tissue has been investigated and specifically considered a therapeutic strategy in inflammatory bowel disease. PPAR α activation suppresses inflammatory process through a variety of mechanisms including tumor necrosis factor-alpha (TNF- α), interleukin (IL)-6, and IL-1 β (Decara et al. 2020).

Anti-inflammatory effects of the primary alkaloid in white mulberry leaf (DNJ) were similarly demonstrated in patients with cardiovascular disease in which a number of inflammatory markers (e.g., hs-CRP, IL-6, TNF- α) were reduced and antioxidant markers (e.g. SOD) were increased (Lim et al. 2013; Ma et al. 2019; Zhang et al. 2022, among others).

Adverse Effects in Clinical Trials

A systematic review of clinical trials of white mulberry leaf for regulating blood sugar levels was conducted, and represents a fairly comprehensive assessment of the data to date (Jeong et al. 2022). Thirteen trials were included in the review. Of these, mild gastrointestinal adverse events including nausea, loose stool, constipation, proteinuria, and abdominal symptoms such as cramping, bloating, flatulence, and distension were reported as occurring in seven studies, though only five publications reporting adverse events were listed (Asai et al. 2011; Lown 2017; Riche 2017; Thaipitakwonga et al. 2020; Yang 2006). The studies of Asai et al. (2011) and Thaipitakwonga et al. (2020) reported on two studies each; Kimura et al. (2007) also reported on two studies. Following is a review of the adverse effects profile reported in the individual studies plus another five that were not included in the Jeong et al. (2022) review.



The first study reported in the review of Jeong et al. (2022) is that of Lown et al. (2017). Contrary to the conclusions presented by Jeong et al. (2022), Lown et al. (2017) reported the following:

“There were no statistically significant differences between any of the 4 groups in the odds of experiencing one or more gastrointestinal symptoms (nausea, abdominal cramping, distension or flatulence).”

The actual data presented in the Lown et al. (2017) study confirms this conclusion showing that more subjects in the placebo group experienced a greater degree of nausea than in the group using the highest dose of mulberry.

A second study by Thaipitakwonga et al. (2020) was a small 12-week trial to determine optimal dosing of DNJ as well as to assess efficacy and safety in healthy and obese diabetic subjects. Adverse events were based on participant self-reporting and investigator survey. Adverse events most commonly reported were gastrointestinal symptoms including bloating, flatulence, and loose stools and occurred in a dose-dependent manner. In the investigation of healthy individuals, 22 subjects were randomized to receive either 0, 2.3, 4.6, or 6.9 g mulberry leaf powder yielding 0, 6, 12, or 18 mg DNJ, three times daily, in conjunction with a sucrose injection. A single individual in the group receiving 4.6 g of mulberry powder and three in those receiving 6.9 g experienced bloating and flatulence. A single individual in the group receiving 6.9 g experienced loose stools. The events were reported as “tolerated” by the study participants and no serious adverse events or changes in hepatic or renal parameters were observed. The dose considered optimal was 4.6 g (12 mg DNJ) specifically to decrease the potential for GI side effects. The authors cite a study by Li et al. (2016) that investigated the blood-sugar-regulating effects of mulberry twig and explain that gas and bloating can be caused by increased osmotic pressure due to white mulberry inhibiting the digestion of carbohydrates, one of the mechanisms of action of white mulberry in reducing sugar absorption. While 50% of subjects experienced some bloating during the first four weeks, the symptoms were mild enough to continue and the

incidence declined over time. As the study was on mulberry twig, the effects cannot inherently be considered present with the leaf.

In a study by Asai 2011, adverse effects were checked by self-report and interview. “No serious adverse events were observed over the study period (including in the withdrawn and excluded subjects). Although the cause of two adverse events (abdominal distension and modest proteinuria) could not be ascertained, both events were observed in the placebo subjects. Several anthropometric and blood measurements changed during the study period in both groups; however, no significant differences were observed between the groups (treatment versus placebo) at any time-point. Gastrointestinal symptoms, such as abdominal distension, diarrhea and flatulence, are the most frequent adverse events of antihyperglycemic medications (e.g., acarbose), which commonly causes a high withdrawal rate of acarbose in diabetic trials (Chiasson et al. 2002). The lack of these symptoms in mulberry leaf studies suggests a high degree of safety and tolerability of mulberry leaf extract.

In a study by Riche (2017), 24 participants were included and equally allocated to receive placebo or mulberry. Of subjects enrolled, 17 completed the study and were included in the intention to treat analysis. The most commonly reported adverse effects were gastrointestinal (gas, stomach upset). However, there was no difference in gastrointestinal adverse effects between treatment and placebo groups. Similarly, no significant adverse effects were observed for body weight, blood pressure, AST, ALT, bicarbonate or serum electrolytes (potassium, sodium, chloride, and calcium) between the treatment and placebo groups.

A final study of Yang (2006) reported by Jeong et al. (2022) as including gastrointestinal adverse effects is in Korean, and was not assessable at the time of this review but states that no hepatotoxicity was reported.

While the review of Jeong et al. (2022), report that white mulberry extract results in gastrointestinal adverse effects, the individual studies suggest that the adverse effects profile between treatment and placebo groups were similar and symptoms experienced were generally mild and tolerable by subjects. The reports of gastrointestinal adverse events reported in the Jeong et al. (2022) study, may have

been used by the county coroner to conclude that mulberry could have contributed or caused this event.

No serious adverse effects from white mulberry leaf were reported in another meta-analysis of 13 studies involving 436 participants (Phimarn et al. 2017).

Single Dose Studies

In a double-blind, randomized, placebo-controlled crossover study in healthy subjects (n=36), ingestion of mulberry leaf extract (250 mg standardized to 4.5-5.5% DNJ) with sucrose (a disaccharide sugar) showed a reduction in blood glucose (not dropping below fasting levels) and plasma insulin levels as determined by capillary blood samples. There was a 42% decrease in blood glucose for the mulberry leaf extract as compared to the control. There were no serious adverse events or adverse events during this study (Thondre et al. 2021).

A randomized, single blind, controlled, crossover clinical trial investigated the impact of orally administered mulberry leaf extract on starch digestion and absorption in healthy subjects (n=25). The treatment was given as a digestible starch wafer containing 1,800 mg mulberry leaf extract standardized to 2% DNJ, or 36 mg DNJ per wafer, taken concomitantly with a high carbohydrate test meal (50 g cornflakes). A non-invasive ¹³C breath test was used to evaluate starch digestion and absorption. Results show a trending decrease in starch digestion and absorption from the beginning of the test which became statistically significant compared to the placebo at 120 min and continued until the end of the test at 240 min. No side effects were reported from the study subjects during and after the study (Józefczuk et al. 2017).

A placebo controlled clinical study examined the effect of mulberry leaf tea and plain tea on post-prandial hyperglycemia in diabetic patients (n=48). During the intervention, blood glucose levels were examined before (fasting) and 90 minutes after consuming a standard breakfast along with mulberry leaf tea (70 mL prepared using one teaspoon of '*Mulbericha green*') or the same amount of normal tea. Postprandial blood sugar was significantly lower for the mulberry leaf tea group compared to the placebo with a large size effect. Adverse events were not reported (Banu et al. 2015).

Repeat Dose Studies

In a clinical study with a within-subjects design, subjects with mild dyslipidemia (n=23) were orally administered mulberry leaf extract (280 mg containing 0.367 mg DNJ) three times a day before meals for 12 weeks. Testing parameters included a routine blood analysis, fasting plasma glucose, and liver function tests. A significant decrease in serum triglyceride was observed at four weeks compared to baseline with significant reductions in total cholesterol, triglyceride, and LDL and an increase in HDL at 12 weeks compared to baseline. There was no difference in dietary composition of macronutrients with protein, carbohydrate, and fat intake remaining stable over the course of the study. Safety was evaluated by liver function tests and the presence or absence of adverse events. The results show no significant difference between pre- and post-treatment in liver enzymes. Severe adverse events were not observed in any of the patients. However, six of 23 subjects experienced mild diarrhea; two patients experienced dizziness but good appetites; one patient experienced dizziness but good appetite; and one patient experienced constipation and bloating. All of these adverse events were mild and occurred and disappeared in the first week of treatment (Aramwit et al. 2011).

In open-label, single-group clinical study, male subjects with relatively high serum triglycerides (≥ 200 mg/dl, n=10) were orally administered mulberry leaf extract (12 mg/dose DNJ) three times daily before each meal (i.e., 36 mg/day DNJ) for 12 weeks. Outcome parameters included hematologic tests, blood biochemical tests, special tests for adiponectin, leptin, ApoB, and lipoprotein, and urinalysis. No significant reduction in serum TG, total cholesterol, LDL, or HDL we observed. The lipoprotein fraction of chylomicron-TG significantly decreased at 12 weeks compared to baseline, but the fraction of VLDL-TG did not significantly decrease. Large, medium, and small LDL were significantly increased at 12 weeks compared to baseline, but very small LDL was significantly decreased. There was a significant reduction in VLDL at 12 weeks compared to baseline, but an increase in LDL and HDL. Levels of adiponectin, leptin, and ApoB were significantly decreased at 12 weeks compared to baseline. Laboratory



parameters showed no change indicative of an adverse event, although the mean levels of blood urea nitrogen and Na were significantly increased at weeks six and 12 compared to baseline; however, all of these were slight changes within reference range with no clinical significance. Reported events included a total of five events in two subjects including soft stools, nasal congestion/headache, myalgia, pharyngeal pain/cough, and fever. All of these events were mild in severity and considered by the investigator to be unrelated to the test food (Kojima et al. 2010).

Pre-Clinical Research

In pre-clinical research, white mulberry leaf and some of its constituents have predominantly been found to beneficially modulate a myriad of physiological processes associated with diabetes, cardiovascular disease, and metabolic syndrome. Some of these activities include a reduction of enzymes associated with hepatic gluconeogenesis and glycogenolysis such as glucose-6-phosphatase (G-6-ase), fructose 1,6-diphosphatase (FDPase), and phosphoenol-pyruvate carboxy kinase (PEPCK) (Li and Ji 2011). Other activities include significant inhibition of mammalian processes influencing glucose metabolism (e.g., decreased α -glucosidase) by binding to enzyme receptors that mimic natural substrates (Asano et al. 2001; Tian et al. 2016). Other mechanisms of white mulberry leaf extract that positively influence diabetes are associated with polysaccharides that protect of pancreatic islet cells from apoptosis by improving Bcl-2/Bax ratio, a marker of insulin resistant diabetes (Li and Zeng 2012). Numerous other mechanisms play a role in the effects of white mulberry leaf beneficially affecting blood sugar regulation. For a more comprehensive review, see Tian et al. (2016).

Collectively, the clinical and pre-clinical data provides no mechanistic plausibility that white mulberry leaf caused or contributed to this fatality.

Toxicological Studies, Reviews and Opinion of Experts

There are a number of formal toxicological studies establishing a high degree of safety for white mulberry leaf and its extracts (water and water:ethanol) at the concentrations



used. There are no reports of acute, chronic, or genotoxic effects, and similarly, no negative changes in hematological, biochemical, or histopathological parameters. There are also no reports suggesting white mulberry leaf is allergenic or increases inflammatory responses, though it is conceivable that any individual can have sensitivity to anything at some time. In contrast, there are numerous pharmacological studies demonstrating neuroprotective, renal protective, and hepatoprotective effects in injury-induction experiments, making it highly unlikely to be a causative agent for gastroenteritis. In animal studies, even high doses of white mulberry leaf have a high degree of safety.

Human Toxicological Studies

In one human safety study, a concentration of 3,600 mg/day of mulberry leaf extract for 38 days did not show any adverse effects in healthy participants (Kimura et al. 2007). Another human pilot study demonstrated mulberry leaf extract at 3,000 mg/day for three months to be safe for consumption in diabetic subjects (Riche et al. 2017). A few other studies reported on biochemical parameters with no remarkable findings regarding vital signs, biochemistry, hematology, liver enzymes, and ECG (Aramwit et al. 2011; Kojima et al. 2010; Wang et al. 2018).

Animal Toxicity Studies

Large Amounts as Fodder

As an example of the safety of mulberry leaf when used as fodder in very large amounts, no adverse effects in milking cows or changes in the yield or butterfat content of milk were observed after animals were fed up to 6 kg of white mulberry leaf daily for 100 days (Srivastava et al. 2003). In two different studies, no adverse effects were observed in rats fed diets containing 1%, 5%, or 25% powdered white mulberry leaf daily for four weeks. Additionally, no abnormalities in organ weights, hematologic and biochemical values, and pathological examination were observed (Mitsuya et al. 2001; Srivastava et al. 2003).

In one feeding study, pregnant sheep fed a diet of 30% or 50% white mulberry leaf in addition to hay for three months, no effects on birth weight were observed (Prasad et al. 1995).

No-Observed-Adverse-Effect Level (NOAELs) and Lethal Doses (LD₅₀s)

Mulberry leaf extract was studied toxicologically in male and female SD rats. The extract was administered orally at concentrations of 0% (control group), 0.1%, 0.4%, and 1% in basal diet for 90 days. No remarkable change in test animals of both sexes was observed in terms of body weight gain or at necropsy. Hematology and blood chemistry revealed no abnormalities. Pathological examination revealed no toxic change in any organ observed. These findings indicate that dietary intake of 1% mulberry leaf extract for 90 days (884.5 mg/kg/day for males and 995.7 mg/kg/day for females as mean daily intake) causes no toxicological change in rats. (Miyazawa et al. 2003).

In a toxicological investigation of a water extract of mulberry leaf, no adverse effects were observed in mice and rats administered a single intraperitoneal dose of 4 and 5 g/kg, respectively. In a subchronic toxicity study by the same investigators, no significant changes in hematological and histological values of major organs were observed at doses of 1, 2, and 3 g/kg/day for 60 days. Signs of central nervous and respiratory system depression were observed, but all animals were recovered within 15 to 30 minutes (Sabsung 2004). This is one of the only studies that suggest any potential for a type of adverse event that conceivably could be associated with a fatality but occurred at concentrations magnitudes higher than what can be approximated to be consumed by the decedent.

In another investigation, conducted according to OECD 407 guidelines in Wistar rats (10/sex/group), a water extract of white mulberry leaf standardized to 5% 1-deoxynojirimycin administered to rats for 28 days at doses of 0, 1,000, 2,000, or 4,000 mg/kg demonstrated no abnormalities in body weight/weight gain, food consumption, ophthalmoscopy, clinical pathology, gross pathology, organ weights, or histopathology. The NOAEL was determined to be 4,000 mg/kg, which was the highest dose tested (Marx et al. 2016).

An acute toxicity study in animals demonstrated no deaths after intraperitoneal administration of doses of 300 and 2,000 mg/kg body weight (bw) for 14 days. This is a very large amount by equivalent human standards and demonstrates an exceptionally high degree of safety. While some biochemical parameters were negatively affected with intraperitoneal administration, no such adverse effects were observed with oral administration (Oliveira et al. 2016). A similar lack of acute toxicity was reported for even higher doses after intragastric administration of 1,000, 2,000 and 4,000 mg/kg (bw) for 28 days (Figueredo et al. 2018). In another safety study, no significant changes in body weight, hematological indexes, functions, and histology of livers and kidneys of rats were observed with oral administration of 1.2 and 3.6 g/kg. However, at the highest dose, diarrhea was observed in 20% of rats (Ahn et al. 2022). This is one of the only studies that suggests a potential for diarrhea, as is implicated in the fatality. However, based on this, the amount administered to rats was equivalent to 42 g in humans, or more than 10 times the typical 3 g dose consumed in formal clinical trials and more than 250 times the approximated 167 mg leaf fragment found in the contents of the stomach of the deceased.

Li et al. (2018) conducted acute, subacute toxicity, and genotoxicity studies of a mulberry leaf water extract in animals. In the acute toxicity assessment, no mortality or behavioral changes were observed after gavage feeding of 15.0 g/kg, establishing the no-observed-adverse-effect level (NOAEL) as greater than 15.0 g/kg. In the subacute assessment, 1.88, 3.75, and 7.50 g/kg were administered by gavage. No significant hematological, biochemical, or histopathological changes were observed establishing a NOAEL of 7.50 g/kg. In the genotoxicity assessment, no mutagenicity, chromosome aberrations, or sperm abnormalities were observed at concentrations of 10 g/kg (Li et al. 2018).

In the study of de Oliveira et al. (2015), ethanolic extract of white mulberry leaves exhibited low oral toxicity with no deaths occurring at a dose of 2,000 mg/kg. At the 300 mg/kg dose, no toxicity or irreversible cellular damage was observed but changes in the proportion of leukocyte types occurred. At the highest concentration, the extract



promoted changes in biochemical, hematological, and histopathological parameters (de Oliveira et al. 2015), reflecting an approximate human dose of 23 g.

An in vivo genotoxicity study of a mulberry leaf ethanolic extract was conducted in male Swiss mice (n=5 per treatment and control group) according to OECD 474 guidelines. The extract was orally administered at doses of 75, 150, and 300 mg/kg 48 hours prior to a blood draw from the orbital plexus. No statistically significant difference in the number of micronucleated polychromatic erythrocytes in the mulberry leaf extract groups compared to the control was observed (de Oliveira et al. 2016).

In one cytotoxicity study, a methanolic extract of white mulberry leaf was found to be non-cytotoxic in the Vitotox assay at concentrations up to 1 mg/mL (Chichioco-Hernandez et al. 2011).

Botanical Safety Handbook (BSH) Review

A formal safety review of white mulberry leaf was conducted by a multi-disciplinary cohort of medicinal plant experts representing botany, traditional herbal medicine, medicine, pharmacology, and toxicology and published in the *Botanical Safety Handbook* (McGuffin and Gardner 2013; CRC Press, American Herbal Products Association). This is widely considered as the most comprehensive and critically reviewed work on the safety of botanical ingredients to date. In the 2013 edition of the BSH, white mulberry leaf is assigned a safety rating of 1 and an interaction rating of A. These ratings are defined based on the committee finding no reports of clinically relevant adverse effects in reviewing the traditional and scientific literature up until 2013 when the text was released, and there was no knowledge of such adverse effects occurring by the team involved in that safety review, several of whom have decades of clinical experience using white mulberry leaf. Additionally, the BSH white mulberry leaf entry was updated (July 2022) prior to the release of the current report of alleged fatality and then reviewed again. While this recent event was considered and reviewed in detail, the committee found there was no compelling evidence to suggest that mulberry leaf caused or contributed to the event and found no additional information that warranted a change in either the Safety or Interaction ratings.



Assessment of Scientific Experts

In addition to the opinions of traditional Chinese medicine Experts expressed previously, other experts in medicine, pharmacology, and toxicology were consulted. According to Bill Gurley, Principal Scientist at the National Center for Natural Product Research, and a specialist in pharmacology, pharmacokinetics, and herb-drug interactions;

“This was obviously an acute event. Toxicological research demonstrates that no acute toxicity is observed in animals given up to 4,000 or 5,000 mg/kg of white mulberry leaf intraperitoneally. When anyone in pharmacy sees this, we consider that substance to be exceedingly safe. The decedent reportedly had caffeine in her system. Given the scientific evidence from the medical literature, caffeine’s diuretic effect far surpasses that of white mulberry leaf. The likelihood of a partial white mulberry leaf causing lethal dehydration does not rise to the level of a reasonable degree of medical or scientific certainty.”... it [mulberry leaf] is “probably one of the safest leaves in the world; its track record for safety is unsurpassed.”

The United Kingdom has long had a robust system for investigating potential adverse reactions due to herbal products. Toxicologist Dr. Debbie Shaw was one of the primary investigators of reported toxicological events working within the National Poisons Information Service (United Kingdom) and with toxicology specialists in China, Australia, and the World Health Organization in Sweden. According to Dr. Shaw;

“In the time that I was investigating adverse effects of herbal ingredients and products, I can recall no adverse reaction reports of white mulberry leaf that would lead me to believe that it could have caused or contributed to such a dramatic and tragic outcome. We have always considered mulberry leaf to have a great degree of safety and it has not been associated with extreme emetic or purgative actions as suggestive of the coroner’s report. There are



many other potentially causative factors that would have to be ruled out through a formal assessment process, including, for example exclusion of heavy metal, viral, and bacterial contamination, in addition to a full toxicological screen, before judgement of causality could be made. A fragment of leaf present in the stomach is not proof of causality.”

Subsequent to the first KHN article, writer Samantha Young, author of the original article, reached out to numerous botanical and medical experts all of whom attested to the non-toxicity of white mulberry leaf. Many also questioned the basis upon which causality was determined, including Dr. James Gill, chair of the College of American Pathologists’ Forensic Pathology Committee and chief medical examiner of Connecticut who stated;

“It can take days for someone to die of dehydration. One leaf alone, which hadn’t been fully digested, a process that usually takes only a couple of hours, would not have contributed to death. It takes about at least a week or so for someone to die from not drinking from dehydration. Based on the available records, there are some things that really don’t fit.”

The writer Ms. Young, attempted to reach out to the county coroner’s office for information on how causality was determined, writing;

“But Sacramento County Coroner Kimberly Gin has not explained — nor provided records that explain — why she determined white mulberry leaf led to the dehydration that killed McClintock at age 61, fueling skepticism among a variety of experts... Gin, contacted through Sacramento County spokesperson Kim Nava, repeatedly declined interview requests from KHN and has refused to provide information that explains how her office concluded that a partial white mulberry leaf contributed to McClintock’s death” (Young 2022b).



Young (2022b) goes on to report that of five pathologists interviewed by KHN, only “one of them said it was plausible that white mulberry leaf could have contributed to the dehydration”, which means four did not express that view, and “All the pathologists said that the coroner’s publicly released documents didn’t provide a complete picture of how McClintock died...” (Young 2022b).

Self-Affirmation of Generally Recognized as Safe (GRAS)

In addition to the formal toxicological studies and BSH safety review, an independent expert panel prepared a formal Self Affirmation of GRAS dossier for select commercial mulberry products characterized to 1% and 5% of the iminosugar piperidine alkaloid iminosugar 1-deoxynojirimycin (DNJ). The panel of experts determined the extracts to be GRAS for their intended use (AIBMR 2016).

Pharmacovigilance Data

Worldwide, governments monitor adverse effects of a variety of substances including modern and traditional (herbal) medicines and foods. Poison control center data and the CAERS Database of the Food and Drug Administration (FDA) in the US reflect pharmacovigilance monitoring in the US. Between 2018 and 2021, only five consumers reported having symptoms from any white mulberry leaf product, most of which were determined by poison control center toxicology specialists to be “non-toxic” and “minimal” and there were no reports of life threatening symptoms or reports of deaths. Specifically regarding mulberry leaf, the clinical managing director of the poison control centers, Kaitlyn Brown, was quoted as follows in the initial KHN article;

“Generally white mulberry as a plant is pretty safe and have a lower order or risk of human toxicity” (Young 2022a).



In the regulation of natural health products in Canada, the Canada Vigilance Adverse Reaction Database is the primary pharmacovigilance reporting system. Between 1965 and 2022, there were a total of seven reports of adverse events that included mulberry among ingredients in products that were ingested. In none of these events was mulberry taken alone. In four of the reports, multiple other products including conventional medications, were taken. In one case, 11 medications were reported taken by one subject. The ingestion of multiple ingredient products prevents any determination of an adverse effect due to mulberry leaf. The ingestion of multiple products makes any association with a botanical impossible to distinguish from an adverse reaction to conventional medications. Of these, the main product taken that contained mulberry leaf as a primary ingredient combined it with a green coffee bean extract (135 mg; caffeine source). In two of the reports, the adverse effects reported (cardiac and sleep disturbances) were more consistent with caffeine effects than anything reported for mulberry leaf. The use of multiple products in the US adverse events reports are generally consistent with those of Canada.

AHP communicated with numerous individuals in the European Union, United Kingdom, Mainland China, and Hong Kong, including specialists in traditional Chinese medicine and toxicology. No one interviewed could recount any instance of any suspected toxicities associated with white mulberry leaf use. There are numerous reviews of mulberry leaf safety in the Chinese language literature that report a lack of toxicity associated with its use.

The most revealing lack of mulberry leaf toxicity comes from Asia where it is used as a food, health supplement, and medicine in hospitals and where active monitoring systems with hospital use occurs. According to Dr. Eric Brand, a specialist in Chinese herbal pharmacy from Hong Kong Baptist University and an expert in the authentication and quality assessment of Chinese herbal drugs;

“Mulberry leaf has a long history of use in Chinese medicine, with few apparent adverse events. According to a randomized sampling of two million recent Chinese herbal medicine prescriptions from Taiwan's electronic medical health records, mulberry leaf is ranked #96 out of 300



individual herbal medicines in terms of its prescription frequency. Data from Taiwan's EMR system shows that a prominent herbal formula containing mulberry leaf [sang ju yin; 桑菊饮] ranks #16 of the top 300 most frequently prescribed herbal formulas by TCM physicians, with over 17,000 kilograms of its concentrated extract prescribed annually. Despite this volume of use, regional pharmacovigilance efforts such as the Taiwan Adverse Drug Reaction Reporting System for Herbal Medicine have not identified prominent adverse events associated with mulberry leaf use.”

ASSESSMENT OF REPORT OF FATALITY

Coroner's Report

The original postmortem of the victim was performed December 16, 2021. The initial cause of death was listed as “pending”. On February 21, 2022, the Chief Coroner of Sacramento County reported the cause of death was dehydration and gastroenteritis due to “Adverse Effects of White Mulberry Ingestion” due to the presence of a leaf fragment found in the victim’s stomach. AHP did not subject the pathological findings to an independent pathology review. However, the section of the autopsy report entitled **Gastrointestinal Findings** reports no remarkable findings regarding the tissues of the stomach, intestines, or colon, which appear incongruent with tissues that were inflamed to a degree to cause severe dehydration and death.

Another potentially anomalous finding is that, presumably, the small fragment of leaf was the only solid particle in the victim’s stomach. The only other content of the stomach reported was “50 cc of tan fluid.” Mulberry leaves are stiff and rough. Attempting to swallow even fragments of fresh or dry leaves of the size reported (1 1/8 x 1 7/8 inches), immediately stimulates the gag reflex. The only way for a leaf of such a size to be swallowed would be if consumed in a soup or a bolus of food, in which case, other stomach contents would be present. The likelihood that mulberry leaf is served as a food in Elk Grove, CA is extremely low.



Determining Causality

Typically, a determination of causality is made after an investigation following specific guidelines such as the Naranjo Score, Bradford Hill Criteria, or WHO criteria (for example see Table 1). Ruling a substance responsible for a toxic event typically requires documentation that the substance has the potential to cause such a reaction. These assessments are done using a variety of formal metrics that consider timing, predictability, independent factors, and provide a scientific basis for the determination. There is no indication that any formal assessment for determining causality was conducted by any of the health officials involved. Based on WHO assessment criteria, minimally, such an event would likely be considered as Unassessable or Unclassifiable as no evidence was provided by which a determination of certainty, probability, or possibility was provided in any of the available documents.

The determination implicating white mulberry leaf was apparently solely due to the reported presence of a “partial plant leaf” in the stomach of the deceased and perhaps the unfamiliarity of the leaf to the examiners who considered that sufficient to assign causality. The presence of a substance in the stomach is not sufficient to make a determination regarding causality but must be considered incidental to the event unless there is a definitive temporal, predictive, independent, or scientifically verifiable basis for the event. There is no indication that any of these criteria were met. Additionally, the ability to identify a partial leaf fragment after it has been exposed to gastric acid is also very difficult and may lack definitiveness.

Table 1 WHO UMC Causality Categories

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

Other Common Causes of Gastroenteritis Not Ruled Out

No indication was given that other common causes of gastroenteritis and/or dehydration were ruled out. The primary causes of gastroenteritis are viral (stomach flu) and bacterial (food poisoning). Viral flu is typically associated with a rotavirus or norovirus but has also been a common occurrence with COVID, for which the decedent tested negative. Additionally, according to a recent study reported in the *American Journal of Emergency Medicine*, moderate to severe gastrointestinal symptoms including



abdominal pain (>52%), diarrhea (~62%), dyspepsia (~28%), and/or nausea (4.7%), occurred within one day in more than 30% of those receiving a first COVID vaccination (Lee et al. 2022). The vaccination history of the decedent was not reported, and perhaps should have been considered in order to rule out anomalous but potential causes.

The most common causes of bacterial gastroenteritis are *Salmonella*, *Campylobacter*, and *E. coli* (e.g. 0157:H7) (Brubaker et al. 2021; Rhodes 2007; White et al. 2019). Typical sources of bacterial gastroenteritis include raw or undercooked meat, poultry, and eggs or egg products, unpasteurized milk, and uncooked vegetables. Other sources of potential bacterial exposure that can cause gastroenteritis include contaminated swimming pools or fecal contamination from sources such as unwashed hands or changing diapers. Excessive consumption of acidic foods such as tomatoes and citrus can similarly cause gastroenteritis, while a variety of diets including Atkins, keto, and paleo are linked to increased risk of dehydration. According to the family, the decedent had “just joined a gym” and was “carefully dieting” (Young 2022). Beyond the potential for exposure from gym pools, hot tubs, and saunas, dehydration itself is common among dieters who strive to lose water weight by restricting fluid and nutritional intake, while at the same exercising. All of these are potential relatively common factors that seemingly were not ruled out. There is a chance for vegetable matter (e.g., a leaf) to be a source of bacterial exposure. However, it was reported that the decedent had experienced stomach upset the day before her death. Stomach contents typically empty within 1.5 to two hours after ingestion. If something else acutely stimulated an inflammatory response, it may no longer have been present in the stomach at the time of the autopsy.

BOTANICAL IDENTIFICATION OF LEAF FRAGMENT AND CONCLUSIONS OF BOTANICAL INVESTIGATORS

Identification

The identity of the fragment of leaf that was the subject of investigation was tentatively made by botanists at the University of California-Davis and a report was issued to the



American Herbal Pharmacopoeia®

Supervising Deputy Coroner's office. The investigation was well done and the language accurately reflects the challenges of making such determinations. Specifically, the report describes that a fragment of the center portion of a leaf approximately 1 1/8" x 1 7/8" was assessed. For those familiar with forensic botany, very seldom can the identity of such a small plant fragment be determined with definitiveness through morphological features, especially after exposure to gastric juices. The conclusion reached by the analysts must be considered tentative and is accurately stated; the leaf "**matched the morphological characteristics of white mulberry leaf**" [emphasis added]... and further lacked characteristics of other species of potentially lethal plants that occur in the area of Elk Grove, Sacramento County, CA. The same features can also be a match for other species of mulberry (e.g., *Morus nigra*, *M. rubra*) as well as other species of plants. One of the key features used to identify the fragment was the presence of a "bronchiostomous loop", which also occurs in the leaves of the highly toxic ornamental *Aristolochia*, resulting in an identification that lacks definitiveness.

According to Iris Solorzano and Elan Sudberg from Alkemist Labs, Garden Grove, CA, specialists in medicinal plant identification;

"The characteristics used to identify the leaf examined are not unique to this genus and species. Many leaves have the same characteristics. Key identifying features of white mulberry leaves include large cells with cystoliths and parenchymatous cells filled with abundant prisms and clusters of calcium oxalate. Few medicinal herbs have both of those features and are unique to white mulberry leaf. Unfortunately, the characteristics reported for the leaf fragment in question were not definitively diagnostic."

The potential lack of definitiveness of the identification of white mulberry leaf was echoed by botanist Christine Leon, an honorary research associate at the Royal Botanic Gardens, Kew in the United Kingdom. Dr. Leon is a specialist in the identification of Chinese medicinal plants and co-author, with Lin Yulin, of one of the most scholarly texts



on Chinese medicinal plant identification in the English language (see Leon and Lin 2017) and reviewed the botanical identification report;

"It is unlikely that a partially intact leaf from stomach contents could be identified with any confidence as that of white mulberry leaf (*Morus alba* L.), even by an expert botanist, based on its morphological characters alone."

Additionally, white mulberry leaves often have white tufts of trichomes in the axils of the midvein and primary lateral veins on the lower surface of the leaf (Leon and Lin 2017). These were not noted as present in the botanical identification report, though these may no longer be observable after leaves soak in gastric juices. There is the possibility that the leaf fragment was of white mulberry, or other *Morus* species of which there are three primary species and dozens of cultivars, but may have been from a different plant.

Reported as Fresh Leaf

The UC Davis botanical identification report suggested the leaf was ingested fresh, due to the observation of its green color and flexibility. The leaf could have been fresh or dry, as rehydration of a previously dried leaf can be equally as flexible as a fresh leaf. In December, mulberry leaves in Northern California, in general, are yellowing; this is reflected in the botanical identification report. High quality material in Asia is picked in autumn after the leaves have yellowed, but may be green if harvested earlier.

Fresh or Dry Mulberry Leaf: Difficult to Swallow Without Mastication

It is highly unlikely that a fresh leaf was consumed as they are generally not available in markets, nor are they commonly served in foods outside of Asia. It is possible that a specialty market, such as in Chinatown, could offer fresh mulberry leaves for sale, but it remains unlikely. Trees in gardens and nurseries are the most likely source of fresh mulberry leaves. However, non-fruiting white mulberry trees are more often used for



American Herbal Pharmacopoeia®

ornamentals along streets whereas fruiting red (*Morus rubra*) or black (*Morus nigra*) mulberry trees are commonly used in gardens and orchards and grown for their fruits.

Fresh mulberry leaves are tough and rough to the oral mucosa unless masticated, at which time they become mucilaginous, but do not retain their intact form. When even chewed even a little, the leaves become mucilaginous and are easy to swallow, but readily break apart and do not remain intact. When intact fresh or dry, a piece that is 1 1/8" by 1 7/8", the size of the fragment as stated in the botanical report, cannot be swallowed by itself without initiating a gag reflex. Alternatively, it is conceivable that if a fresh or dry white mulberry leaf was cooked with food, that such a fragment could have been swallowed within a bolus of food, which would result in other solid contents in the stomach being reported but were absent. When dry, there is less of a mucilaginous quality.

AHP Assessment of Mulberry Leaves

AHP inspected leaves from two different varieties of mulberry grown in the AHP garden in Soquel, CA as well as dried white mulberry leaves imported from China. The smallest leaf on mature AHP trees in September 2022 was 10 cm long (base to apex) by 5 cm broad; the largest was 15 cm by 15 cm (4.2 x 2.1 and 6.5 x 6.5 inches, respectively). The dry leaf of each averaged 300 mg for the small-leafed variety and 873 mg for the larger variety leaf. A large dry white mulberry leaf imported from China measured up to 18 cm x 13 cm (7.25 x 5.25 inches) and weighed approximately 775 mg. Fragments of each approximating the 1 1/8" x 1 7/8" fragments reported in the UC Davis botany report weighed 120, 167, and 96 mg, for the small-leaf variety, large-leaf variety, and Chinese sample, respectively (see Figure 4 above). This is far below doses used as food, in health supplements, and in medicines historically and in formal clinical and toxicological investigations, and based on all that is known about the botanical, should have been of no toxicological consequence in this event.



American Herbal Pharmacopoeia®

Botanical Analysts Inform Coroner—“White mulberry is not toxic”

The UC Davis report of botanical identity was presented to the Sacramento Coroner’s office and stated; “White mulberry is not toxic.” Based on the information that has been made publicly available there is no indication of why the investigating and certifying authorities disregarded the opinion of botanical experts in alleging that a fragment of a leaf of a presumptively non-toxic plant was the cause of death. The opinion of the UC Davis botanists regarding the lack of toxicity of mulberry leaf is consistent with the accumulated literature that attests to its safety.

MEDIA REPORTING OF EVENT—FATALITY CAUSED BY A “HERBAL REMEDY” OR “DIETARY SUPPLEMENT”

Kaiser Health News (KHN)

The original report of KHN announced that the death was due to an “Herbal Remedy” “Marketed for Diabetes and Weight Loss” and suggested that the supplement industry was insufficiently regulated, because they “don’t undergo the rigorous scientific and safety testing the government requires of prescription drugs and over-the-counter medicines.” Specifically, the original KHN piece promoted legislative initiatives such as mandatory product registration proposed by Senator Richard Durbin, perhaps the most ardent and longest-standing opponent of health supplements in the Senate. Product registration is based on the premise that FDA does not know how many supplements there are, and according to the article, “making it almost impossible for the government to oversee them and punish bad actors”, a claim that appears to be without substantiation.

Current regulations require for all involved in the manufacture or holding of supplements to be registered with FDA precisely so they can be found should the need arise. According to Holly Bayne, a Washington, DC-based attorney specializing in food and drug law:

“In the 25 years I have been in legal practice, I am not aware of any case in which FDA identified a public health or safety problem but could not



locate the responsible company. Dietary supplement manufacturers and those engaged in packaging and holding operations must register their facilities with FDA. Also, dietary supplements must include a domestic address or phone number on the label through which adverse events can be reported. If a dietary supplement company cannot be found with reasonable effort, this would suggest blatant non-compliance that no additional regulations will correct. While some industry critics and media outlets continue to express concern that the industry is insufficiently regulated, FDA has ample enforcement authority to remove unsafe or illegal products from the marketplace under existing laws and regulations and has for decades.”

Every industry, including pharmaceuticals, is subject to fraud. In 2009, the pharmaceutical giant Pfizer plead guilty to a felony charge and agreed to pay \$2.3 billion in fines for the fraudulent marketing of select drugs (DOJ 2009) and in 2018, paid fines for illegal business practices (DOJ 2018). Another pharmaceutical giant Johnson and Johnson, settled a legal case for \$5 billion for the role they played in the emergence of the opioid crisis that has claimed more than 800,000 lives (Raymond 2020). This was accompanied by 65 additional fines or settlements in which Johnson and Johnson paid out more than \$14 billion since 2000 (GJF 2022) demonstrating that this is a recurring pattern within the most heavily governmentally regulated industry. The suggestion as proposed in the popular media articles that regulating supplements similarly to pharmaceuticals will prevent fraud is largely unsound. Those who commit fraud willfully circumvent laws and require continued enforcement of the laws that already exist. The harm done by individual pharmaceuticals, such as opioids or even acetaminophen (Tylenol) which is one of the leading causes of liver failure worldwide, has been greater than any damage done by the entire class of herbal medicines or supplements historically or in modern times. Ironically, the nutritional supplement N-acetyl cysteine remains the primary therapy to protect against acetaminophen-induced liver toxicity (Jaeschke et al. 2020). Sufficient laws governing the manufacturing and marketing of



American Herbal Pharmacopoeia®

supplements already exist yet many are sadly unfamiliar with the benefits that supplements have to offer, and instead, express fear such as reflected in the media coverage of this tragic event.

The KHN article echoes arguments for greater restrictions over supplements that are typical of physicians and other practitioners of conventional medicine who are more familiar with the manner in which pharmaceutical medications and medical devices are regulated, and less familiar with the regulation of foods and supplements. Conventional health care practitioners are typically unaware of the manner in which traditional herbal medicines and phytomedicines are regulated in many countries throughout the world. More importantly, the commentary is reflective of general lack of knowledge regarding the regulatory requirements to which manufacturers, distributors and marketers of dietary supplements in the US must adhere.

The content of the original KHN article was subsequently widely disseminated and repurposed uncritically by a variety of news media. For example, contrary to the KHN headline, supplements are prohibited from being marketed for diseases such as diabetes; weight loss claims must be appropriately qualified to ensure they are substantiated. Any product marketed with a disease claim that has not been approved by FDA as a “drug”, is not in compliance with an OTC drug monograph, or fails to comply with the regulatory requirements for “health claims” is subject to regulatory action by FDA as an illegal drug, and the Federal Trade Commission (FTC) if the claim is unsubstantiated.

All food, herbal, and nutritional ingredients used in dietary supplements are required to be safe. Any ingredient found to be unsafe may be removed from the market by FDA. Supplements must be packaged and labeled as “dietary” or “herbal” supplements and must meet all relevant federal and state regulatory requirements regarding their safety, manufacture, labeling, facility registration, adverse event reporting, and health claim notifications and meet all relevant state and county regulations regarding good business practices and conformity with health codes. To ensure quality, supplement products must be manufactured according to Good Manufacturing Practices (GMPs) as promulgated and enforced by FDA. All supplement



American Herbal Pharmacopoeia®

claims must be truthful, not misleading, scientifically supported, and submitted to FDA for review. Supplements are specifically prohibited from being marketed for diseases such as diabetes and obesity, and weight loss claims must be presented in an appropriate context to ensure the claim is truthful, adequately substantiated, and does not imply that a supplement alone can result in weight loss without any dietary or lifestyle changes (see CHIBNI 2003; DSHEA 1994; FALCPA 2004; FSMA 2010; GMPs 2008; PHSBPRA 2002, among others; see Table 2).

The following commentary is intended to address some of the misperceptions expressed in relationship to this reporting.

No Herbal Supplement Implicated

Based on the currently publicly available information, no actual product was reported as consumed. The only indication of what was ingested is from the UC Davis botanical identification report that suggested a fresh leaf was consumed. A fresh leaf can be considered an “herbal remedy” but is not typically a product form marketed as an “herbal” or “dietary supplement”, which is the focus of much of the article’s criticism of the “booming” “\$54 billion industry”. Typically in such events, the decedent’s home is examined for potential remains of the material ingested or other items that may also have been ingested, such as medications or other substances, including substances that may have been consumed unintentionally. No such information was disclosed and there is no evidence suggesting that an actual white mulberry leaf supplement was found.

The coroner’s report stated; “Portions of tablets and capsules cannot be discerned in the stomach”. Tablets and capsules are the most typical dosage forms of herbal supplements. The original KHN report stated; “It’s unclear from the autopsy report whether Lori McClintock took a dietary supplement containing white mulberry leaf, ate fresh or dried leaves, or drank them in a tea...” but somehow supplements became the focal point of the narrative, while other more likely potential causes of death were not explored.



American Herbal Pharmacopoeia®

Table 2 Primary laws and regulations governing the manufacture, marketing, and distribution of dietary supplements

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT (DSHEA) 1994	
	FDA maintains authority to remove unsafe ingredients and supplements from the market.
	Requires conformity with GMP regulations under the regulatory and inspectional authority of FDA.
	Requires adherence to product labeling laws that include full ingredient disclosure, appropriate directions for use and precautions, listing of a responsible company for traceability to brand holder, and a domestic address or phone number through which adverse events may be reported.
	Prohibits disease claims, whether express or implied.
	Allows for health-related claims commonly known as structure-function claims, provided they are truthful, non-misleading, and supported by reliable scientific evidence relevant to the claim. Structure-function claims must be submitted to FDA within the first 30 days of marketing and are reviewed by FDA to determine whether the claim is a disease claim or permissible supplement claim.
	New dietary ingredients (NDIs) require FDA pre-market notification and submission of safety data, at least 75 days in advance of marketing the NDI in a supplement.
FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT (FDAMA) 1997	
	Premarket authorization process for health claims based on an authoritative statement by a scientific body of the US with official responsibility for public health protection or research directly related to human nutrition or National Academy of Sciences.
PUBLIC HEALTH SECURITY AND BIOTERRORISM PREPAREDNESS AND RESPONSE ACT (PHSBPRA) 2002	
	Requires all food and dietary supplement manufacturers and holding facilities to be registered with FDA and requires importers to provide advance notification to FDA of raw material and finished product imports.
CONSUMER HEALTH INFORMATION FOR BETTER NUTRITION INITIATIVE (CHIBNI) 2003	
	Advances FDA's implementation of the regulatory framework required for the potential allowance of "qualified health claims".



American Herbal Pharmacopoeia®

<p>Anabolic Steroid Control Act amendment (ASCA) 2004</p> <p>Bans steroid precursors to be sold as or in dietary supplements.</p>
<p>FOOD ALLERGEN LABELING AND CONSUMER PROTECTION ACT (FALCPA) 2004</p> <p>Requires ingredient disclosure of major allergens that cause 90% of food allergies.</p>
<p>DIETARY SUPPLEMENT AND NONPRESCRIPTION DRUG CONSUMER PROTECTION ACT 2006</p> <p>Requires reporting to FDA of all serious adverse events for both dietary supplements and over the counter drugs and record-keeping of all adverse event reports according to standard operating procedures, all of which are subject to FDA inspection</p>
<p>GOOD MANUFACTURING PRACTICES (GMPs) 2010</p> <p>Requires compliance with GMPs under the regulatory authority of FDA per 21 C.F.R. Part 111; governs dietary ingredients and finished dietary supplements, product safety and quality; manufacturers must ensure dietary supplements meet established specifications for identity, purity, strength, composition, and lack of contaminants that could adulterate the product; own-label distributors are responsible for ensuring all specifications are met and supplements are produced, packaged and labeled in conformance with GMPs.</p>
<p>FOOD SAFETY MODERNIZATION ACT (FSMA) 2010</p> <p>Provides FDA with enhanced mandatory recall authority for all foods (other than infant formula) and dietary supplements.</p>
<p>Expands food and dietary supplement facility registration requirements, imposes supply chain foreign supplier verification requirements on imported raw materials and finished foods and supplements, and authorizes FDA to establish Hazard Analysis and Risk-Based-Based Preventive Controls (HARPC) rules.</p>

Supplement Safety: Perception Versus Reality

The KHN article stated; “[Mrs.] “McClintock’s death underscores the risks of the vast, booming market of dietary supplements and herbal remedies”. As there was no dietary supplement product implicated commentary such as this is unfortunate and misrepresents the facts of the case that others repeat. Of greater relevance is that it



does not accurately reflect the safety of herbal remedies or nutritional supplements when looking at use and safety data worldwide.

As noted, it is a federal requirement under DSHEA that all ingredients must be safe or may not be used in dietary supplements. Though there is not a master list of acceptable ingredients, all ingredients that were in the food chain prior to the enactment of DSHEA in 1994, were presumed safe due to a relative lack of toxic events associated with them. If new information regarding the potential toxicity of a supplement ingredient emerges, FDA maintains the authority to remove the ingredient from the market. New dietary ingredients require prior approval by FDA that includes a formal safety review of the ingredient.

Most relevant is that when the safety data of various categories of regulated goods is compared, including foods, supplements, and pharmaceutical medications, supplements are the lowest in terms of incidences of adverse effects and deaths. If we add other regulated goods for which adverse effects are known, most notably alcohol, tobacco, and firearms, it is difficult to understand how the misperception of supplement ingredients being unsafe emerged as a consistent narrative within the conventional medical community. Each year approximately 450 deaths are attributed to acetaminophen (Tylenol) and it remains a major cause of liver failure worldwide. Approximately 46,000 die annually from opioids in the US (NIDA 2022), approximately 128,000 die from properly prescribed and used medications, including in hospitals, the most well-controlled of all prescribing settings, and FDA-approved pharmaceuticals result in approximately 2.74 million serious adverse drug reactions (FDA 2018; Light 2014). In 2010, there were 38,329 reported drug overdose deaths in the United States, most (22,134) were associated with pharmaceutical medications (Jones et al. 2013). In contrast, in the same year (2010), the annual report of the American Association of Poison Control Centers reported zero deaths due to dietary supplements in adult use, and a single unconfirmed death due to a pediatric exposure (Bronstein et al. 2011). Unfortunately, despite this marked disparity, there continues to be a consistent misperception among conventional health professionals regarding the safety of herbal and nutritional supplements.



In contrast, most pharmaceutical medications have a relatively narrow therapeutic index that carries with them an array of side effects, even when they are used properly. Most are synthesized in a laboratory and have never been subject to any human use so must be treated very differently than foods and botanical ingredients for which centuries of human use exist. A consistent pattern of fatalities and serious adverse effects associated with fully approved and properly used pharmaceutical medications has been reported in the medical literature for decades. In the US, as well as in other countries, pharmaceutical medications are the third and fourth leading causes of preventable deaths (see Budnitz et al. 2006; CDC 2017; Classen et al. 1997; FDA 2018; Jones et al. 2013; Kohn et al. 1999; Lazarou et al. 1998; Leape et al. 1991; Light 2014; Wolfe et al. 2018, among others). Meanwhile, the preponderance of evidence supporting the high degree of safety of herbal products, when used properly, has similarly been a matter of public record and the conclusion of experts for decades (Bronstein et al. 2011; Edwards 1997; Farnsworth 1993).

Approximately 80% of Americans use some type of supplement, primarily out of a desire to stay well or be healthier, partly to address health issues not adequately addressed in conventional care, to take an active role in their own health outcomes, and partly out of a desire to avoid potentially harmful synthetic medications. Despite widespread use of supplements, adverse events are rare, and when they occur, with rare exceptions, are generally mild.

Misrepresentation of Scientific Data

The original KHN article states; “White mulberry leaf can have side effects, including nausea and diarrhea” and further quotes Dr. D'Michelle DuPre, a retired forensic pathologist and a former medical examiner in South Carolina who stated;

[white mulberry leaves "do tend to cause dehydration, and part of the uses for that can be to help someone lose weight, mostly through fluid loss, which in this case was just kind of excessive."



The only scientific reference provided in the article is by Lown et al. (2017). This is an article investigating the blood sugar regulating effects of white mulberry, which additionally looked at the side effect profile of those taking mulberry and those taking placebo. Contrary to the information presented, the Lown et al. (2017) study itself states that there were no statistically significant differences in adverse effects between study subjects taking white mulberry and those taking placebo. In the Lown et al. (2017) study, more individuals taking placebo experienced gastrointestinal symptoms than those taking the highest dose of mulberry (see review of Clinical Trials above). We find no evidence that mulberry leaves cause or contribute to dehydration.

The article also presents information on adverse effect reports made to FDA that were associated with white mulberry leaf, two of which were presumably of toxicological relevance, stating: “Since 2004, two cases of people sickened by mulberry supplements have been reported to the FDA”.

This similarly represents a misunderstanding of reporting systems. A report made to such reporting systems do not establish causality but rather are meant to identify signals of potential public health hazards that may warrant FDA attention. Had those two reports been followed with numerous others within a relatively short period of time, further investigation may be warranted. However, two reports in an 18-year period (2004-2022) is not suggestive of any toxicological signaling. However, for completeness, the actual reports were obtained through a *Freedom of Information Act* request. In one of the cases (Report #104496), the product taken contained 12 ingredients, in which, mulberry leaf was the second to the lowest amount, and the individual was taking four other supplement products including a multivitamin, which often have more than 20 nutritional or botanical ingredients. Moreover, she had several co-morbidities including low blood pressure, blood clots, diabetes, heart attack, and gall bladder and kidney dysfunction, and she was taking the cardiovascular medication Lanoxin digoxin). The patient herself suggested she had a allergy to pine and that perhaps the microcrystalline cellulose excipients used in the supplements were made from pine. No association with mulberry leaf could be made in such a case. In the second (Report #128655), which was very poorly organized, the subject experienced

“intermittent numbness on her left side since 2008”; the report was submitted in 2010. In addition to taking a supplement that presumably contained white mulberry leaf but is actually not listed, the subject was taking several medications, including Naprosyn, lisinopril, Ultram, aspirin, Evista, hydrochlorothiazide, and two antibiotics. It is obvious that no association between mulberry leaf and “someone being “sickened” could be drawn from such a report. Additionally, the report states the subject may be suffering from trans ischemic strokes (TIAs) and she was on medications (Lisinopril, hydrochlorothiazide) specifically to control blood pressure and reduce the risk of stroke.

CONCLUSION

When tragic events such as this occur, it is contingent upon all involved in the process of investigating and reporting, to be clear, accurate, and responsible in understanding all aspects of the event. This is the only way for similar tragedies to be avoided, and it is also important to provide family members an accurate assessment of what happened. There are no words to assuage the loss of a loved one, and our hearts go out to the family members.

The coroner’s report provides no reasoning for how causality was assigned to white mulberry leaf, when the historical and scientific literature clearly establishes its safety. Similarly, there is no explanation of how other more common causes of gastroenteritis were ruled out, a necessity of an appropriate forensic investigation. Regarding the identity of the leaf fragment, a definitive conclusion cannot be reached, by no fault of the investigators, but by the fact that only a small fragment of a portion of a leaf after exposure to gastric juices was available for examination. Leaves of other species of plants, including some that are highly toxic and not used medicinally, possess the same general characteristics. Mulberry leaf also has unique structural features that were not examined, which would have increased the definitiveness of the identification.

The estimated weight of the fragment found in stomach contents (~167 mg) is far below the therapeutic dose of 4.6 g (yielding ~12 mg DNJ) that is typical and well established as safe in clinical studies. Formal toxicological investigations of mulberry



leaf in humans reveal mulberry leaf to be safe in doses exceeding 3,600 mg. Mulberry leaf has been consumed as a food ingredient in Asia for generations, and consumed as part of COVID prevention programs since the initial outbreak of SARS in China in 2002, ranks in the highest third regarding prevalence of use, without any signals of overt toxicity. A review of pharmacovigilance data as well as communications with experts in the US, Canada, United Kingdom, Hong Kong, China, and Taiwan, similarly reveal no adverse effects signaling that indicate white mulberry leaf to possess the level of toxicity required to either cause or contribute to such an adverse event.

Formal toxicological data in animals reveals that doses of up to 4,000 mg/kg lack adverse effects. A review of the pharmacological data gives no suggestion that white mulberry leaf and its constituents possess pharmacological activity that would be consistent with either being causative or contributory to the event. Finally, the opinion of experts in the use of mulberry leaf reveals no suggestion of toxic potential even in large doses.

An unfortunate consequence of the initial KHN report is the manner in which this event was used to disparage the entire category of supplements, when there appears to be no supplement that was involved in this event. Worldwide, people use supplements and herbal remedies to prevent disease, to treat or improve conditions not adequately addressed by conventional medical strategies, and to improve their health. Health care providers in the US are unique in the world in not recognizing the immense value of natural healing strategies in human health. Because of the general unfamiliarity of botanicals among pathologists, medical doctors, pharmacists, and other medical investigators, there is often an unfounded perception of danger. Conversely, pharmaceuticals have been one of the leading causes of preventable deaths for decades, in the US and in other countries (see Budnitz et al. 2006; CDC 2017; Classen et al. 1997; FDA 2018; Jones et al. 2013; Kohn et al. 1999; Lazarou et al. 1998; Leape et al. 1991; Light 2014; Wolfe et al. 2018, among others), which in part, drives consumer use of supplements. The United States is unique among nations in not acknowledging the value of natural health products as an integral part of natural health care systems. While the regulation of foods, and herbal and nutritional supplements is



different from the regulation of pharmaceutical medications and medical devices, this is consistent worldwide as most foods, nutritional, and herbal supplements have been in the public domain, sometimes for literally thousands of years, for which there exists a tremendous amount of data regarding their use and safety, and generally speaking, their therapeutic index is very wide. In contrast, conventional medicines are most often synthesized with no historical use of safety or efficacy, have very narrow therapeutic indices, and include a myriad of adverse effects, even when used properly. Predictably, disparaging the benefits of supplements in modern health care is a common theme of the conventional medical community. Moreover, some of the scientific literature reported as evidence of potential mulberry toxicity misrepresented what the scientific data actually reported.

To assign causality of a serious adverse event to any substance requires that a formal review, following formal guidelines for determining causality, be employed. FDA, WHO, and a myriad of such formal processes exist, but there is no indication that any were followed. The mere presence of something at time of death is not sufficient to draw a conclusion of either causality or contribution. White mulberry leaf has a more than 1800-year record of safe use for promoting health, with formal empirical, clinical, and toxicological evidence demonstrating its safety. The formal clinical and toxicological investigations of white mulberry leaf span a period of more than 20 years, in a myriad of countries, all reporting consistent findings regarding safety.

References

- [ASPCA] American Society for the Prevention of Cruelty to Animals. 2022. Mulberry tree. Pet Care, Animal Poison Control, Toxic and Non-Toxic Plants. <https://www.asPCA.org/pet-care/animal-poison-control/toxic-and-non-toxic-plants/mulberry-tree>. Accessed 9.13.22
- [CDC] Centers for Disease Control and Prevention. 2017. Adverse drug events in adults [file:///Users/royu/Desktop/Adverse%20Drug%20Events%20in%20Adults%20 %20Medication%20Safety%20Program%20 %20CDC.html](file:///Users/royu/Desktop/Adverse%20Drug%20Events%20in%20Adults%20%20Medication%20Safety%20Program%20%20CDC.html)
- [DOJ] Department of Justice. 2009. Justice department announces largest health care fraud settlement in its history. September 2. <https://www.justice.gov/opa/pr/justice-department-announces-largest-health-care-fraud-settlement-its-history>. Accessed 9.18.22



American Herbal Pharmacopoeia®

- [DOJ] Department of Justice. 2018. Drug maker Pfizer to pay \$23.85 million to resolve false claims act liability for paying kickbacks. May 24.
<https://www.justice.gov/opa/pr/drug-maker-pfizer-agrees-pay-2385-million-resolve-false-claims-act-liability-paying-kickbacks>. Accessed 9.18.22
- [GJF] Good Jobs First. 2022. Violation tracker.
<https://violationtracker.goodjobsfirst.org/parent/johnson-and-johnson> accessed 9.19.22
- [FDA] Food and Drug Administration. 2018. Preventable Adverse Drug Reactions: A focus on drug interactions. <https://www.fda.gov/drugs/drug-interactions-labeling/preventable-adverse-drug-reactions-focus-drug-interactions> Accessed 9.15.22
- [HKBU] Hong Kong Baptist University. Chinese Medicinal Material Images Database. Accessed 9 Sep 2022:
<https://sys01.lib.hkbu.edu.hk/cmed/mmid/detail.php?qry=morus%20alba&sort=name&lang=eng&page=1&pid=B00334>
- [KHP] Korean Herbal Pharmacopoeia. 2002. 4th English ed. Seoul, Korea Food and Drug Administration.
- [MOH] Ministry of Health. 2002. List of materials traditionally recognized as both food and Chinese herbal medicine. Ministry of Health, People's Republic of China.
- [PPRC] Pharmacopoeia of the Peoples Republic of China. 2015 (English edition). Beijing: China Medical Science Pr. 2185 p.
- [THP] Taiwan Herbal Pharmacopoeia. 2019. 3rd ed. Taiwan: Ministry of Health and Welfare. 438 p.
- Ahn PTV, Hang VV, Ngoan DT. 2022. Safety evaluation of mulberry powder: Assessment of subchronic toxicity in rats. JMR 154 E10 (6):1-9.
- AIBMR. 2016. The generally recognized as safe (GRAS) status of Reducose™ 5%. Expert panel report. AIBMR Life Sciences. 45.
- Andallu B, Suryakantham V. 2001. Effect of mulberry (*Morus indica* L.) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes. Clin Chim Acta 314: 47-53.
- Aramwit P, Petcharat K, Supasyndh O. 2011. Efficacy of mulberry leaf tablets in patients with mild dyslipidemia. Phytotherapy Research 25(3): 365–369.
<https://doi.org/10.1002/ptr.3270>
- Asai K, Nakagawa K, Higuchi O, et al, 2011. Effect of mulberry leaf extract with enriched 1-deoxynojirimycin content on postprandial glycemic control in subjects with impaired glucose metabolism. Journal of Diabetes Investigation 2(4): 318-323.
- Asano N, Yamashita T. 2001. Polyhydroxylated alkaloids isolated from mulberry trees (*Morus alba* L.) and silkworms (*Bombyx mori* L.). J Agric Food Chem 49:4208.
<https://www.frontiersin.org/research-topics/9199-articles>
- Banu S, Jabir NR. 2015. Reduction of post-prandial hyperglycemia by mulberry tea in type-2 diabetes patients. Saudi J Biol Sci. 22:32-36.
- Baronov AI. 1966. Wild vegetables of the Chinese in Manchuria. Econ Bot 21(2):140-155.
- Bastri BN (ed.). 1962. The wealth of India, raw materials. Vol VI. New Delhi: Council of Scientific & Industrial Research. 483.



American Herbal Pharmacopoeia®

- Bensky D, Clavey S, Stoger E. 2004. Chinese herbal medicine: materia medica. 3rd ed. Seattle (WA): Eastland Press. 1311 p.
- Brand E, Wiseman N. 2008. Concise Chinese materia medica. Taos (NM): Paradigm Pub. 540 p.
- Bronstein AC, Spyker DA, Cantilena LR, et al. 2011. 2010 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. Clinical Toxicology 49: 910-941.
- Brubaker J, Zhang XY, Bourgeois AL, et al. 2021. Intestinal and systemic inflammation induced by symptomatic and asymptomatic enterotoxigenic *E. coli* infection and impact on intestinal colonization and ETEC specific immune responses in an experimental human challenge model. Gut Microbes 13(1) e1891852 (13 pages) <https://doi.org/10.1080/19490976.2021.1891852>
- Budnitz DS, Pollock DA, Weidenbach KN, et al. 2006. National surveillance of emergency department visits for outpatient adverse drug events. JAMA, October 18: 296(15): 1858-1866.
- Butt MS, Nazirb A, Sultana MT, et al. 2008. *Morus alba* L. nature's functional tonic. Trends in Food Science & Technology 19: 505-51.
- Chan EWC, Lye PY, Wong SK. 2016. Phytochemistry, pharmacology, and clinical trials of *Morus alba*. Chinese Journal of Natural Medicines, 14(1): 0017-0030 doi: 10.3724/SP.J.1009.2016.00017
- Chang BY, Koo BS, Kim SY. 2021. Pharmacological activities for *Morus alba* L., focusing on the immunostimulatory property from the fruit aqueous extract. Foods 10, 1966. <https://doi.org/10.3390/foods10081966>
- Chemweno 2021. **The U.S. Healthcare System is Broken: A National Perspective.** Managed Healthcare Executive. July 27. <https://www.managedhealthcareexecutive.com/view/the-u-s-healthcare-system-is-broken-a-national-perspective>. Accessed 9.21.22
- Chen J, Chen TT. 2004. Chinese medical herbology and pharmacology. City of Industry: Art of Medicine 1266 p.
- Chiaasson JL, Josse RG, Gomis R, et al. 2002. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 359: 2072-2077.
- Chichioco-Hernandez C, Wudarski J, Gevaert L, et al. 2011. Evaluation of cytotoxicity and genotoxicity of some Philippine medicinal plants. Pharmacogn Mag 7(26):171-5.
- Classen DC, Pestotnik SL, Evans RS, et al. 1997. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA 277(4):301-306.
- Colwell A, Potter D, Doyle J. 2021. The UC Davis Center for Plant Biodiversity; JM Tucker Herbarium. Davis, CA. Dec 29.
- Dat NT, Binh PTX, Quynh LTP, et al. 2010. Cytotoxic prenylated flavonoids from *Morus alba* [L.]. Fitoterapia, 81: 1224-1227.
- Decara J, Rivera P, Lopez, AJ, et al. 2020. Peroxisome proliferator-activated receptors: experimental targeting for the treatment of inflammatory bowel diseases. Front Pharmacol 27 May. doi: 10.3389/fphar.2020.0073
- Deepa M, Sureshkumar T, Satheeshkumar PK, et al. 2013. Antioxidant rich *Morus alba* leaf extract induces apoptosis in human colon and breast cancer cells by the



American Herbal Pharmacopoeia®

- downregulation of nitric oxide produced by inducible nitric oxide synthase. PMID: 23441618 DOI: 10.1080/01635581.2013.748924
- Devitt M. 2001. Supplement use continues to rise in the U.S. *Acupuncture Today* October 2(10): 1-6.
- Doi K, Kojima T, Makino M, et al. 2001. Studies on the constituents of the leaves of *Morus alba* L. *Chem Pharm Bull* 49(2): 151-153.
- Edwards R. 1997. World Health Organization Pharmacovigilance report. European Scientific Cooperative for Phytomedicines. London.
- Farnsworth N. 1993. Utilization of Medicinal Plants, World Health Organization (WHO), Philadelphia.
- Figueredo KC, Guex CG, Reginato FZ, et al. 2018. Safety assessment of *Morus nigra* L. leaves: Acute and subacute oral toxicity studies in Wistar rats. *Journal of Ethnopharmacology* 224 290-296. <https://doi.org/10.1016/j.jep.2018.05.013>
- Gheldof N, Francey C, Rytz A, et al. 2022. Effect of different nutritional supplements on glucose response of complete meals in two crossover studies. *Nutrients* 14: 2674. <https://doi.org/10.3390/nu14132674>
- Gin KD, Fearn E, Tovar JP. 2021. Department of Coroner. County of Sacramento. Case #21-08920. 12.26.21.
- Hassan Fu, Arshad MA, Li MW, et al. 2020. Potential of mulberry leaf biomass and its flavonoids to improve production and health in ruminants: Mechanistic Insights and Prospects. *Animals* 10, 2076; doi:10.3390/ani10112076
- Hu SY. 2005. Food plants of China. Hong Kong: Chinese University Pr. 844 p.
- Hunt L. 2001. Consumers satisfied with supplements, need more information, survey says. *HerbalGram*. 53: 10
- Jaeschke H, Akakpo JY, Umbaugh D, et al.. 2020. Novel therapeutic approaches against acetaminophen-induced liver injury and acute liver failure.
- Jeong HI, Jang S, Kim KH. 2022. *Morus alba* L. for blood sugar management: A systematic review and meta-analysis. *Evid Based Complement Alternat Med* 23:9282154.
- Jones CM, Mack KA, Paulozzi LJ. 2013. Pharmaceutical Overdose Deaths, United States. 2010. *Research Letters. JAMA* February 20; 309(7): 657-659.
- Józefczuk J, Malikowska K, Glapa A, et al. 2017. Mulberry leaf extract decreases digestion and absorption of starch in healthy subjects—A randomized, placebo-controlled, crossover study. *Advances in Medical Sciences* 62(2):302–306. <https://doi.org/10.1016/j.advms.2017.03.002>
- Kandylis K, Hadjigeorgiou I, Harizanis P. 2009. The nutritive value of mulberry leaves (*Morus alba*) as a feed supplement for sheep. *Trop Anim Health Prod* 41:17-24 DOI 10.1007/s11250-008-9149-y
- Kim ES, Park SJ, Lee EJ, et al. 1999. Purification and characterization of moran 20K from *Morus alba*. *Arch Pharm Res* 22: 9-12.
- Kim SY, Gao JJ, Lee WC, et al. 1999. Antioxidative flavonoids from the leaves of *Morus alba*. *Archives of Pharmacal Research* 22(1):81-85
- Kimura T, Nakagawa K, Kubota H, et al. 2007. Food-grade mulberry powder enriched with 1-deoxynojirimycin suppresses the elevation of postprandial blood glucose in humans. *J Agric Food Chem* 55: 5869-5874.



American Herbal Pharmacopoeia®

- Klimko M. 2016. Micromorphology and anatomy of leaves of *Morus alba* L. Moraceae cultivars from Poland. *Steciana* 20(2): 73-83.
- Kohn KT, Corrigan JM, Donaldson MS. 1999. *To Err Is Human: Building a Safer Health System*. National Academy Press, Washington, DC. 312.
- Kojima Y, Kimura T, Nakagawa K, et al. 2010. Effects of mulberry leaf extract rich in 1-deoxynojirimycin on blood lipid profiles in humans. *Journal of Clinical Biochemistry and Nutrition*, 47(2): 155-161. <https://doi.org/10.3164/jcbrn.10-53>
- Lafont R, Dinan L. 2013. Practical uses for ecdysteroids in mammals including humans: An update. *J Insect Sci* 3(7): 1-30.
- Lau TF, Leung PC, Wong ELY, et al. 2005. Using herbal medicine as a means of prevention experience during the SARS crisis. *The American Journal of Chinese Medicine* 33(03): 345-356.
- Lazarou J, Pomeranz BH, Corey PN. 1998. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 279(15):1200-5.
- Leape LL, Brennan TA Laird N, et al. 1991. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 324(6):377-384.
- Lee DS, Kim JW, Lee KL, et al. 2022. Significance of digestive symptoms after COVID-19 vaccination: A retrospective single-center study. *The American Journal of Emergency Medicine* 58: 154-158.
- Leon C, Lin YL. 2017. *Chinese medicinal plants, herbal drugs and substitutes: an identification guide*. Royal Botanic Gardens, Kew (UK). Kew Publishing. 806 p.
- Li M, Huang X, Ye H, et al. 2016. Randomized, double-blinded, double-dummy, active-randomized, double-blinded, double-dummy, active-controlled, and multiple-dose clinical study comparing the efficacy and safety of mulberry twig (*Ramulus Mori*, Sangzhi) alkaloid tablet and acarbose in individuals with type 2 diabetes mellitus. *Evid Based Complement Alternat Med* 7121356.
- Li SZ. 1596. *Ben cao gang mu* (compendium of materia medica). Volume V. Beijing: Foreign Language Pr. 3714 p. 2003 translation.
- Li X, Zeng X. 2012. Active constituents of hypoglycemic part from *Morus alba* L. *Cent S Pharm* 4:245-248.
- Li Y, Ji D. 2011. Hybrid of 1-deoxynojirimycin and polysaccharide from mulberry leaves treat diabetes mellitus by activating PDX-1/insulin-1 signaling pathway and regulating the expression of glucokinase, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in alloxan-induced diabetic mice. *J Ethnopharmacol* 134:961-970.
- Li Y, Zhang X, Liang C, et al. 2018. Safety evaluation of mulberry leaf extract: Acute, subacute toxicity and genotoxicity studies. *Regul Toxicol Pharmacol* 95:220-226.
- Lian AR (ed). 2001. *Zhong yao cai se xian wei tu jian* (Colored microscopic illustration of authenticated Chinese medicines). Beijing. Chinese Medicine Sciences Publications. 250.
- Light DW. 2014. New prescription drugs: A major health risk with few offsetting advantages. Edmond & Lily Safra Center for Ethics, Harvard University. June 27. <https://ethics.harvard.edu/blog/new-prescription-drugs-major-health-risk-few-offsetting-advantages>



American Herbal Pharmacopoeia®

- Lim HH, Yang SJ, Kim Y, et al. 2013. Combined treatment of mulberry leaf and fruit extract ameliorates obesity-related inflammation and oxidative stress in high fat diet-induced obese mice. *J Med Food* 16: 673-680.
- Lown M, Fuller R, Lightowler H, et al. 2017. Mulberry-extract improves glucose tolerance and decreases insulin concentrations in normoglycaemic adults: Results of a randomised double-blind placebo-controlled study. *Free PMC article* 16:486. doi: 10.1186/s13063-015-0997-2.
- Ma GQ, Chai XY, Hou GG, Zhao FG, Meng QG. 2022. Phytochemistry, bioactivities and future prospects of mulberry leaves: A review. *Food Chemistry* 372 (2022) 131335.
- Ma Y, Lv W, Gu Y, et al. 2019. 1-Deoxynojirimycin in mulberry (*Morus indica* L.) leaves ameliorates stable angina pectoris in patients with coronary heart disease by Improving antioxidant and anti-inflammatory capacities. *Front Pharmacol* 21 May <https://doi.org/10.3389/fphar.2019.00569>
- Marx TK, Glávits R, Endres JR, et al. 2016. A 28-day repeated dose toxicological study of an aqueous extract of *Morus alba* L. *Int J Toxicol* 35(6):683-691.
- McGuffin M, Gardner (eds). 2013. Botanical safety handbook. 2nd edition. Boca Raton (FL), CRC Press. 1035.
- Mitsuya M, Suegara N, Kojima Y, et al. 2001. Four-week oral toxicity studies of the leaf powder of mulberry (*Morus alba* L.) in rats. *Pharmacometrics* 61(1):169-176.
- Miyazawa M, Miyahara C, Satoh S et al. 2003. Ninety-day dietary toxicity study of mulberry leaf extract in rats. *Shokuhin Eiseigaku Zasshi* 44(4):191-197.
- Mohammadi J, Naik PR. 2008. Evaluation of hypoglycemic effect of *Morus alba* in an animal model. *Indian J Pharmacol* 40(1):15-8.
- Mudra M, Ercan-Fang N. 2007. Influence of mulberry leaf extract on the blood glucose and breath hydrogen response to ingestion of 75 g sucrose by type 2 diabetic and control subjects. *Diabetes Care* 30:1272-1274.
- National Academies. 2013. U.S. health in international perspective. Shorter lives. Poorer health. National Academies of Sciences, Engineering, Medicine. <https://nap.nationalacademies.org/download/13497>. Accessed 9.21.22
- Oliveira AMD, Mesquita MdS, da Silva GC, et al. 2015. Evaluation of toxicity and antimicrobial activity of an ethanolic extract from leaves of *Morus alba* L. (Moraceae). *J Evid Based Complementary Altern Med* 2015:513978.
- Oliveira AMD, Nascimento MF, Ferreira MR, et al. 2016. Evaluation of acute toxicity, genotoxicity and inhibitory effect on acute inflammation of an ethanol extract of *Morus alba* L. (Moraceae) in mice. *J Ethnopharmacol* 24;194:162-168.
- Park MY, Lee KS. 2005. Effects of dietary mulberry, Korean red ginseng, and banaba on glucose homeostasis in relation to PPAR-alpha, PPAR-gamma, and LPL mRNA expressions. *Life Sci* 77: 3344-3354.
- Phimarn W, Wichaiyo K, Silpsavikul K, et al. 2017. A meta-analysis of efficacy of *Morus alba* Linn. to improve blood glucose and lipid profile. *Eur J Nutr* 56(4):1509-1521.
- Pieroni A, Söukand R, Bussmann RW. 2020. The inextricable link between food and linguistic diversity: Wild food plants among diverse minorities in Northeast Georgia, Caucasus. *Econ Bot* 74(4):379-397.
- Prasad PE, Reddy DN, Reddy MR, et al. 1995. Effect of feeding mulberry (*Morus alba*) hay in the rations to pregnant ewes. *Indian J Anim Nutr* 12(2):109-111.



American Herbal Pharmacopoeia®

- Raymond N. 2020. J&J to contribute up to \$5 billion to potential U.S. opioid settlement. Reuters. Oct 18. <https://www.reuters.com/article/usa-opioids-johnson-johnson/jj-to-contribute-up-to-5-billion-to-potential-u-s-opioid-settlement-idUSKBN26Y2PA>. Accessed 11.2.21
- Rhodes JM. 2007. The role of *Escherichia coli* in inflammatory bowel disease. Gut 56(5):610-612. doi: 10.1136/gut.2006.11187.
- Riche DM, Riche KD, East, HE, et al. 2017. Impact of mulberry leaf extract on type 2 diabetes (Mul-DM): a randomized, placebo-controlled pilot study. Complementary Therapies in Medicine 32:105-108.
- Rogers A, Fearn E, Kasirye O. 2022. Certification of Vital Record [3052021313629]. State of California. Department of Health and Human Services. Issued July 19.
- Sabsung A, Phornchirasilp S, Luanratana O, et al. 2004. A toxicity study of *Morus alba* L. leaf extract. Thai Journal of Pharmacology. 26(1): Conference abstract. P13: 70.
- Saluga S, Woolhandler S, McCormick, et al. 2016. Unsafe drugs were prescribed more than one hundred million times in the United States before being recalled. International Journal of Health Sciences 46(3) <https://doi.org/10.1177/002073141665466>
- Shahana S, Pratima A, Nikalje G. 2019. Phytochemistry and bioactivity of *Morus alba* (mulberry) plant: A comprehensive review. Asian Journal of Pharmacy and Pharmacology 5(2):207-21.
- Song W, Wang HJ, Buchell P, et al. 2009. Phytochemical profiles of different mulberry (*Morus* sp.) species from China. J Agric Food Chem 57(19):9133-40
- Srivastava S, Kapoor R, Thathola A, et al. 2003. Mulberry (*Morus alba*) leaves as human food: a new dimension of sericulture. Int J Food Sci Nutr 54(6):411-416.
- Srivastava S, Kapoor R, Thathola A, et al. 2006. Nutritional quality of leaves of some genotypes of mulberry (*Morus alba*). Int J Food Sci Nutr 57(5-6):305-13.
- Sujathamma P, Savithri G, Kavyasudha K. 2013. Value addition of mulberry (*Morus* spp.). International Journal of Emerging Technologies in Computational and Applied Sciences (IJETCAS). 13-365.
- Sujathamma P, Savithri G. 2016. Scenario of Indian sericulture. Econ Soc Sci 6: 113-119.
- Tang W, Eisenbrand G. 1992. Chinese drugs of plant origin, Springer-Verlag, Berlin, Heidelberg, New York. 1056.
- Thaipitakwong T, Supasyndh O, Rasmi Y et al. 2020. A randomized controlled study of dose-finding, efficacy, and safety of mulberry leaves on glycemic profiles in obese persons with borderline diabetes. Complement Ther Med 49:102292.
- Thondre PS, Lightowler H, Ahlstrom L, et al. 2021. Mulberry leaf extract improves glycaemic response and insulaemic response to sucrose in healthy subjects: Results of a randomized, double blind, placebo-controlled study. Nutrition & Metabolism, 18(1): 41. <https://doi.org/10.1186/s12986-021-00571-2>
- Tian S, Tang M, Zhao B. 2016. Current anti-diabetes mechanisms and clinical trials using *Morus alba* L. J Tradit Chin Med Sci 3:3-8.
- Wagner H, Bauer R, Melchart D, et al. 2011. Chromatographic fingerprint analysis of herbal medicines. Volumes 1,2. New York: Springer. 1024 p.



American Herbal Pharmacopoeia®

- Wang R, Li Y, Mu W, et al. 2018. Mulberry leaf extract reduces the glycemic indexes of four common dietary carbohydrates. *Medicine* 97(34): e11996.
<https://doi.org/10.1097/MD.00000000000011996>
- Weil A. 2013. U.S. manages disease, not health. CNN March 10.
<https://www.cnn.com/2013/03/08/opinion/weil-health-care>. Accessed 9.21.22
- Wen LR, Shi DD, Zhou T, et al. 2020. Identification of two novel prenylated flavonoids in mulberry leaf and their bioactivities. *Food Chem* doi: 10.1016/j.foodchem.126236 Epub 2020 Jan 21.
- White AE, Clampa N, Chen YX, et al. 2019. Characteristics of *Campylobacter*, *Salmonella* infections and acute gastroenteritis in older adults in Australia, Canada, and the United States. *Clin Infect Dis* October 15; 69(9): 1545-1552.
doi:10.1093/cid/ciy1142.
- Wilms S. 2017. The divine farmer's classic of materia medica, Shen Nong Ben Cao Jing. Corbett (OR). Happy Goat Productions. 549.
- Wolfe D, Yazdi F, Kanji S, et al. 2018. Incidence, causes, and consequences of preventable adverse drug reactions occurring in inpatients: A systematic review of systematic reviews. *PLoS ONE* 13(10): e0205426. <https://doi.org/10.1371/journal.pone.0205426>
- Woolf SH, Aron L. US health in international perspective: shorter lives, poorer health. National Research Council and Institute of Medicine. US Washington, DC: The National Academies Press; 2013. 420 pp.
- Yang JH, Han JS. 2006. Effect of mulberry leaf extract supplement on blood glucose, glycated hemoglobin and serum lipids in type II diabetic patients, supplement on blood glucose, glycated hemoglobin and serum lipids in type II diabetic patients. *Journal of the Korean Society of Food Science and Nutrition* 35(5): 549-556.
- Yang Y, MDS Islam, Wang J, et al. 2020. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): A review and perspective. *Int J Biol Sci* 16: 1708-1717.
- Young S. 2022a. Congressman's wife died after taking herbal remedy marketed for diabetes and weight loss. *Kaiser Health News*. August 24.
- Young S. 2022b. Experts question the role of white mulberry in the death of congressman's wife. *Kaiser Health News* September 14.
- Zhang RY, Zhang Q, Zhu S, et al. 2022. Mulberry leaf (*Morus alba* L.): A review of its potential influences in mechanisms of action on metabolic diseases. *Pharmacological Research* 175. 106029.
- Zhong L, Furne JK. 2006. An extract of black, green, and mulberry teas causes malabsorption of carbohydrate but not of tri-acylglycerol in healthy volunteers. *Am J Clin Nutr* 84: 551-555.



Biographies of Writers and Reviewers

Compiler

Roy Upton RH DipAyu: Roy is the founder, president, and editor of the American Herbal Pharmacopoeia®. He is trained in Ayurvedic, Chinese, and Western herbal medicine traditions as well as Caribbean and North American ethnobotanical traditions. He has been studying and working professionally as an herbalist since 1981, is a registered herbalist with the American Herbalists Guild, has Diploma in Ayurveda, holds adjunct faculty positions at the University of California-Santa Cruz, Southwest College of Naturopathic Medicine, and Institute of Bencao Gangmu, Beijing, China and serves as editor to numerous journals and formal advisory positions to numerous organizations.

Technical Reviewers

Eric Brand PhD LAc: Dr. Brand earned his PhD in Chinese herbal pharmacy at Hong Kong Baptist University, supervised by Prof. Zhao Zhongzhen, an expert in the authentication of Chinese herbal medicine. Dr. Brand traveled to over 12 countries and 15 provinces in China visiting farms, herbal markets, and factories assessing the quality control of herbal medicines. Dr. Brand is an expert on the botanical authentication of Chinese medicinal plants and history of traditional Chinese herbal medicine. He is an assistant professor at the Taipei Medical University, Taipei, Taiwan and an AHP advisor.

John Chen PhD, OMD, LAc, PharmD: Dr. John Chen is a recognized authority in both western pharmacology and Chinese herbal medicine, having combined formal training in both fields. He has taught at the University of Southern California and University of California San Francisco School of Pharmacy as well as numerous colleges of traditional Chinese medicine. Dr. Chen is an AHP advisor.

Stefan Gafner PhD: Dr. Gafner is the Chief Science Officer of the American Botanical Council, an independent, nonprofit research and education organization. He holds a



degree in pharmacy and a PhD in pharmaceutical sciences, with a focus on the chemistry of medicinal plants.

Thomas Avery Garran PhD: Dr. Garran earned his PhD at the China Academy of Chinese Medical Sciences: National Center for Materia Medica Resources and Daodi Herbs. He has been a practitioner of herbal medicine since 1992 and practitioner of Chinese medicine since 1997. Dr. Garran is an AHP advisor.

Bill Gurley PhD: Dr. Gurley has a PhD in Pharmaceutical Sciences, is the Principal Scientist at the National Center for Natural Product Research, University of Mississippi, and is co-director of the Center for Dietary Supplement Safety Research, University of Arkansas for Medical Sciences, Colleges of Pharmacy and Public Health, Little Rock, Arkansas. Dr. Gurley is an AHP advisor.

Christine Leon PhD: Dr. Leon has worked as a botanist for the Royal Botanic Gardens, Kew in the United Kingdom for 40 years, specializing in the fields of plant conservation, plant toxicology, and traditional Chinese herbal medicine. She was the Research Officer of the Traditional Remedies Surveillance Programme and the Manager of poisonous plants of the UK, jointly with Guy's & St Thomas Hospital, London. Dr. Leon is an expert on the botanical authentication of Chinese medicinal plants and is an AHP advisor.

Elan Sudberg BA: Elan holds a degree in chemistry and is the CEO of Alkemist Labs, a Drug Enforcement Agency schedule 1, 2, 3n, and 4t testing facility specializing in plant authentication, botanical ingredient identification, quantitative analytical services and contaminant screening for foods, beverages, supplements, and cosmetics. Elan is also a specialist in the microscopic assessment of botanical ingredients. Elan is an AHP advisor.



Professor Dr Judith Rollinger: Professor Dr. Rollinger is a professor of pharmacognosy and pharmaceutical biology at the University of Vienna, Austria. She is trained in pharmacy, immunology, and microbiology, was editor of the medicinal plant journal *Planta Medica*, and is the president of the *Society for Medicinal Plants and Natural Product Research* (GA), the primary organization dedicated to medicinal plants in the European Union. She has investigated the chemistry of mulberry for more than 15 years.

Debbie Shaw PhD: Dr. Shaw served as a primary toxicologist with Guys' & St Thomas' National Poisons Information Service (United Kingdom), with a primary role of investigating reports of adverse effects, toxicities, and drug interactions of herbal products specifically to determine relationships of causality, with a specific focus on Chinese herbal medicines. Additionally, she worked with specialists in China, Australia, and with the World Health Organization in Sweden in investigating herbal medicine safety and toxicity. Dr. Shaw is an AHP advisor.

Legislative Review

Holly Bayne JD: Holly is the founder of the Law Office of Bayne & Associates, a Washington DC-based law firm specializing in food, drug and cosmetic law. For the past 25 years, Holly has specialized in matters involving FDA and FTC regulation of foods, dietary supplements, and botanical products.