

# *Aristolochia* Herbs and Iatrogenic Disease: The Case of Portland's Powders

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*Aristolochia* herbals have a 2500-year history of medicinal use. We focused this article on Portland's Powders, an 18<sup>th</sup>-century British gout medicine containing *Aristolochia* herbs. The powders constitute an 18<sup>th</sup>-century iteration of an herbal remedy, which was used, with variations, since at least the fifth century BCE. The use of Portland's Powders in Great Britain may appear to be an unusual choice for investigating a public health problem currently widespread in Asia. Yet it exemplifies long-term medicinal use of *Aristolochia* herbs, reflecting our argument that aristolochic acid nephropathy (AAN) is a historically persistent iatrogenic disease. Moreover, we provide compelling evidence that individuals taking Portland's Powders for gout would have ingested toxic quantities of aristolochic acid, which causes AAN and cancer. Several factors, including long history of use, latency of toxic effects, and lack of effective regulation, perpetuate usage of *Aristolochia* herbals to the present day.

## INTRODUCTION

In the early 1990s, an outbreak of a rapidly progressive and irreversible renal disease among a group of Belgian women heralded the existence of a previously unrecognized global health problem. Subsequently, physicians traced this cluster of cases to a Belgian spa: specifically, to the consumption of *Aristolochia fangchi*, inadvertently substituted for a non-toxic Chinese herb in the clinic's weight-loss regimen [1-3]. All *Aristolochia* herbs analyzed to date contain a potent nephrotoxin and human

carcinogen known as aristolochic acid, which exhibits serious, but delayed toxic effects. Thousands of cases worldwide have recently been reported of what is now known as aristolochic acid nephropathy (AAN) [4-6].

*Aristolochia* species grow on every continent except Antarctica, and have featured in traditional medical systems for more than two thousand years. Despite their demonstrated toxicity, they continue to be used for medicinal purposes, creating a global public health problem. This problem is especially acute in China, where medicinal use of various species of *Aristolochia* was recorded

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Abbreviations: AAN, aristolochic acid nephropathy.

Keywords: aristolochia, aristolochic acid, birthwort, gout, iatrogenic, herbal medicine

Author Contributions: TT conducted historical research and wrote this article. AF conducted analyses of *Aristolochia* herbs. AG developed the concept for the study and helped with revisions.

Dedication: *The authors dedicate this paper to the late Bernard Semmel (Stony Brook University and then the CUNY Graduate Center) who taught us by example that disciplinary boundaries were historically contingent.*

as early as at least the first century CE. The long history of medicinal use and official descriptions of *Aristolochia* spp. in pharmacopoeias document the large-scale exposure to aristolochic acid of populations worldwide [6-10].

Given this background, we posit that AAN is a historically persistent, long-unrecognized iatrogenic disease, resulting directly from medical intervention, which now affects millions of people, especially in China and other Asian countries. This article presents as a case study the medicinal use of a mixture of herbs containing birthwort (here, *Aristolochia rotunda*), that was known in 18<sup>th</sup>-century Britain as Portland's Powders. This may seem an unusual choice for investigating the history of a public health problem currently widespread in Asia. Yet, the powders constitute an 18<sup>th</sup>-century iteration of herbal recipes containing birthwort (a name used interchangeably in the sources for *Aristolochia longa*, *Aristolochia rotunda*, and *Aristolochia clematidis*), which has been used since the fifth century BCE in ancient Greece and Rome to aid women in childbirth and in the treatment of gout [11]. Thus, the powders provide an example of the use of *Aristolochia* herbs in a manner that almost certainly resulted in serious toxicities, especially chronic renal disease.

We show here how the use of Portland's Powders to treat gout over extended periods likely caused AAN centuries before cases of this disease were documented. We develop our argument by tracing the long history in Europe of similar medications for gout. Next, the formula and dosage instructions for Portland's Powders are used to compare potential aristolochic acid exposures to those observed in recent cases of AAN. Our calculations are supplemented with comparative observations of Portland Powders-related symptoms by 18<sup>th</sup>-century and modern physicians, remaining conscious of the limitations and dangers of "retrospective diagnosis [12]." Finally, we note striking similarities between the marketing of herbal medicine in the 18<sup>th</sup>-century and today, both involving largely unregulated use of potentially toxic herbal remedies, then and now posing a significant threat globally to public health [13]. We conclude that *Aristolochia*'s long history of use, latency of toxic effects, and a lack of effective regulation have perpetuated the herb's worldwide usage to this day.

As one history of public health claims, "heroic accounts of the triumphant emancipation of modern society from the primitive bondage of ignorance can no longer be sustained [14]." Nonetheless, progressive assumptions remain embedded in popular narratives of modern medicine and public health. Examining an iatrogenic disease whose effects span 2,000 years reveals common pitfalls of public health policy and practice [15].

## PORTLAND'S POWDERS AND GOUT

Portland's Powders, so-called due to their association with William Bentinck, second Duke of Portland, rocketed to fame in Britain during the 1750s as a cure for gout. A variety of advertisements, testimonials, medical treatises, and self-help guides made mention of the powders, leading to an increase in popularity for this herb in apothecaries' shops. Yet, despite the apparent novelty of Portland's Powders in mid-18<sup>th</sup>-century Britain, a multitude of observers made clear they reprised an old remedy under a new name. For example, Scottish physician John Clephane compared the mixture to recipes in the works of ancient medical authorities, observing "that medicines of this nature have been long known in physic; they were not only in use among the Greek physicians, but made a considerable part of their practice in gouty and arthritic complaints [16]." To support the claim of the powders' long history, Clephane cited a range of ancient medical authorities, as well as more recent ones. Some of the older recipes contain numerous ingredients, making their connection to Portland's Powders somewhat tenuous for modern observers, but still easily recognizable. For example, the "*antidotus podagrica ex duobus centaureae generibus*," in Aetius of Amida's *Tetrabiblos*, appears nearly identical to the Duke of Portland's recipe, which contains equal parts of round birthwort, gentian, germander, ground pine and the tops and leaves of the lesser centauray. Aetius's recipe differs only in omitting the ground pine.

Aetius calls for daily doses of this medication over the course of a year [16,17]. Another physician, Alexander of Tralles (525-605 CE), describes several recipes for medicines containing *Aristolochia* to treat gout. Like Aetius, Alexander prescribes treatment with these medicines for extended periods, usually daily for a year or, in one case, with days off between doses. In addition, one of the medicines contains both *Aristolochia* and gentian while three others contain these ingredients plus centauray and germander [18]. An earlier physician, Proclus (14-37 CE), provides a formula for a gout medication containing germander, centauray, and *Aristolochia* among its ingredients; this medication, too, was meant for extended daily use [19]. Caelius Aurelianus (fl. ca. 450 CE) notes that such bitter tonics were popular for treating gout, and he calls them *annalia medicamina* for their regular use over the course of a year or more [20]. Thus, under various names, including the Duke of Mirandola's powders and, with some recipe alterations, the Duke of Savoy's powders, *Aristolochia* herbs were in wide use in countries across continental Europe throughout the early 18<sup>th</sup> century [16,21].<sup>1</sup>

The directions for using Portland's Powders called for consistent dosing over an extended period, providing

those in the 18<sup>th</sup> century with an additional reason to link the powders to the ancient medicines cited above. Sufferers were instructed to “take one drachm of this mixed powder” daily for three months. The instructions then call for reductions of the dose “to  $\frac{3}{4}$  of a drachm for three months longer”, then six months at  $\frac{1}{2}$  a drachm, and finally a year at this amount taken every other day [16]. One household recipe handbook deviates slightly from the standard directions in setting the duration of the first half drachm period at only three months [22]. Physician John Gardiner equates Portland's Powders to ancient gout medicines like those of Galen, and then provides directions for the older medicines that are identical to the Portland's Powders regimen, save for an initial reduction to two scruples — $\frac{2}{3}$  of a drachm—rather than  $\frac{3}{4}$  of a drachm [23]. Another version from the early 19<sup>th</sup> century omits the three months at  $\frac{3}{4}$  a drachm [24]. Finally, a mid-18<sup>th</sup>-century work claims “the dose, according to the original empirical recipe, was as much as could lie on a shilling, to be taken every morning: but, in a more regular method of administration, it is now one dram [25].” In other words, published instructions for the use of Portland's Powders closely resemble one another, and frequently include a warning that the medication works slowly, indeed “insensibly,” making persistence necessary. As this warning suggests, taking Portland's Powders aimed to cure gout rather than simply mitigate intermittent attacks.

Unsurprisingly, considering the Powders' surge in popularity, many reports claimed to have alleviated or eliminated symptoms of gout; however, these reports often included caveats. By the final third of the 18<sup>th</sup> century, views of Portland's Powders became increasingly negative.

As early as 1754, John Clephane cited the cautions of ancient authorities not to use such powders for too long [16]. According to the 18<sup>th</sup>-century English apothecary and chemist Robert Dossie, Portland's Powders alleviated and often prevented attacks of gout, but “it has been, nevertheless, observed; that in frequent instances, apoplectic, paralytic, or acute diseases followed the cure within a few years, particularly in older subjects [25].” The writer of a 1797 work thought Portland's Powders might be helpful, but that if taken as long as directed, “the remedy would be worse than the disease [26].” The famous and respected physician, William Heberden, the elder, similarly argued that though the powders were beneficial in cases of gout, they produced negative effects when taken at the high doses “indiscriminately given to all [27].” According to physician Alexander Sutherland, “Its indiscriminate use has averted fits of the gout, and substituted mortal or incurable ailments [28].” Sutherland refers to the case of a 40-year-old man who “took Portland's powders strictly,” which ended his fits of gout but caused him to vomit

everything he ingested. The doctors could not help him, and “with his last breath he cursed the powders [28].” Other sources recapitulated the accusation of lethality in equally stark terms. According to one 1804 piece, “it does not appear that there is one instance of their [gout pains] being removed in this way [by following the given directions] in which the patient survived the effects of the medication above a few years [29].”

## TOXICITY OF ARISTOLOCHIA AND PORTLAND'S POWDERS

Aristolochic acid can produce acute toxicity; it is also a cumulative poison. Of the Belgian women who developed AAN in the early 1990s, those who developed chronic renal failure received, on the average, a cumulative dose over the course of a weight-loss regimen of 138+/-16.3 grams of *Aristolochia* [30]. Those who developed end-stage renal disease averaged 192+/-13.1 grams [30]. Thus, on average, we estimate that these women ingested approximately 281.15+/-33.25mg and 391.68+/-26.72mg of aristolochic acid, respectively [31].<sup>2</sup> A recent study in Taiwan concludes that ingestion of aristolochic acid exceeding 150mg is “associated with an increased risk of developing urinary tract cancer,” and notes that lower doses increase the risk of chronic kidney disease [31,32].<sup>3</sup>

It is important to note, as this statement suggests, that aristolochic acid has two major toxicities: chronic renal impairment and cancer. Recent work has posited a link between consumption of *Aristolochia* and various human cancers [33]. Although consuming *Aristolochia* can result in cancer, we have chosen in this paper to focus on renal impairment, largely because current research suggests that aristolochic acid-induced cancer from the doses in Portland's Powders would take 20-40 years to appear—unlike chronic renal impairment from a large dose of aristolochic acid, which would develop much sooner. Given such a delay, contemporary observers probably would not have connected cancers, if they diagnosed them, to use of the powders decades earlier. The same time lag, combined with the insufficiency of extant sources from the period, would render it unlikely for us to be able make such a connection on a significant scale.

Applying our calculations of dosage to the case of Portland's Powders reveals that individuals following the prescribed regimen would have ingested an amount of aristolochic acid associated with significant renal toxicity. A conservative estimate of the quantity of aristolochic acid in the root of *Aristolochia rotunda* is approximately 0.15% by weight [34];<sup>4</sup> thus, daily exposures range from 1.08mg during the first 3 months, to 0.81mg during the second 3 months, to 0.54mg during the final periods. This amounts to ingestion of roughly 365mg of aristolochic

acid over the full course of treatment. Following instructions in the 1810 *Family Receipt-Book*, which is at the low end of the range of published dosages, would result in the ingestion of roughly 291mg of aristolochic acid [24].

Of course, it is difficult to know how faithfully patients followed their instructions; the *Family Receipt-Book* claims that due to impatience “few gouty patients can be induced thus regularly to continue the medicine, as directed, even for half the length of time prescribed [24].” Nonetheless, these dosages are well within the range associated with renal failure, and far above the minimum amount associated with increased cancer risk. If an individual loosely followed the regimen, even halfway, he or she would have received a toxic exposure to aristolochic acid. Further, medical practice in Europe, like practices in other parts of the world, used *Aristolochia* herbs for a variety of acute and chronic conditions. Given aristolochic acid’s cumulative properties, intermittent uses of the herb would have increased basal levels of exposure, thereby lowering the threshold for toxicity from subsequent exposure to aristolochic acid-containing herbal remedies, including Portland’s Powders.

Given the similarities between Portland’s Powders and its ancient antecedents, it is unsurprising that calculations for gout medications from earlier periods show similar results [11]. For example, Proclus, a physician practicing in Rome during the early first century CE, prescribed taking the following composition for 1 year:

9 ounces of germander, 8 ounces of white centaury with fruits still attached, 7 ounces of birthwort brought from the mountains, 6 ounces of imperforated gentian, 5 ounces of St. John’s wort, 3 ounces of parsley, 3 ounces of valerian, 1 ounce of hoof fungus, 2 *kotylai* of honey. Pound in a mortar, and sift/triturate each ingredient separately; then mix them and soften them with honey; pound them and fashion trochisks of one *drachma* each [11,19].

This recipe would have resulted in a daily dose of slightly less than 1mg of aristolochic acid, with a total dose over the prescribed year of 315mg, an amount associated with nephrotoxic and carcinogenic effects.

These calculations, *in toto*, are highly suggestive, but the uncertainty regarding adherence to the Powders regimen points to limitations and potential problems in any retrospective diagnosis. For one thing, nomenclature and measurements present challenges, especially for periods that lacked consistent standardization in these respects. Descriptions of symptoms, in particular, do not always line up with modern interpretations, so one needs to approach them with care. Perhaps most significantly, retrospective diagnosis can reflect and contribute to anachronistic interpretations of the past when seen through modern standards and ideas, potentially blinding

us to the ways in which people in the past perceived and experienced the world. Addressing these issues is important, but does not mean that “informed speculation” concerning disease has no value historically. This article examines a historical case study as a means of explaining ways in which a specific iatrogenic disease has persisted for so long, and to illuminate the historical roots of a current public health challenge [35].<sup>5</sup>

Eighteenth-century condemnations of Portland’s Powders cite a small number of printed sources for support. These offer further support for the argument that using Portland’s Powders exposed people to toxic amounts of aristolochic acid. Chief amongst these are the works of William Cadogan (1711-1797) and, especially, William Cullen (1710-1790). Cadogan, a prominent physician in England, published *A Dissertation on the Gout and on All Chronic Diseases* in 1771 [36]. He sparked heated debate around his argument that indolence, intemperance, and “vexation” caused gout, and that the only cure lay in eliminating these causes [36]. In making this claim, Cadogan attacked supposed medicinal cures for gout as ineffectual or harmful. In what became a widely cited passage, he wrote of Portland’s Powders:

many of those who took it died very soon. I myself observed between fifty and sixty of it’s [*sic*] advocates, some my patients, some my acquaintance or neighbours, who were apparently cured by it; but in less than six years time, *omnes ad interneccionem caesi*, they all died to a man [37].

Unfortunately, Cadogan provides no further detail about his observations, and there appears to be no extant correspondence or unpublished papers he wrote on the topic. Still, the observation of fatalities among a group of people who took the powders is significant, particularly, given the time frame after treatment. The influential Scottish chemist and physician, William Cullen, described specific symptoms—in addition to premature death—that he attributed to taking Portland’s Powders. Like many others, Cullen acknowledged the Powders’ effectiveness in ending the recurrence of “paroxysms of inflammatory gout [38].” Still, he argued that their dangers outweighed their benefits. The following passage is worth quoting at length, for its description of symptoms and for its popularity among subsequent authors to support claims about the deleterious effects of Portland’s Powders:

But I have had occasion to know or to be exactly informed of the fate of nine or ten persons who had taken this medicine for the time prescribed, which is two years...In no instance, however, that I have known, was the health of these persons tolerably entire. Soon after finishing the course of their medicine, they became valetudinary in different shapes; and particularly were much affected with dyspeptic, and what are called nervous complaints, with lowness of spirits. In every one of them, be-



fore a year had passed after finishing the course of the powders, some hydropic symptoms appeared, which gradually increasing in the form of an ascites or hydrothorax, especially the latter joined with anasarca, in less than two or at most three years proved fatal [38].

The same description appears in Cullen's *First Lines of the Practice of Physic*, with the addition of "apoplexy" and "asthma" to the above "dropsy [39]."

These accounts are consistent with recent known cases of AAN, and combined with our dosage calculations, they suggest a direct link. First, Cullen's location of the onset of symptoms after completing the course of medication, and considerably after the toxic dose had been reached, fits closely the pattern of the well-documented cases of Belgian women in the early 1990s. The first two of these women reported to have developed renal failure sought medical treatment months after the end of the weight loss regimen during which they ingested *Aristolochia* [1]. Second, the period within which Cadogan and Cullen report that people who had used Portland's Powders died is consistent with chronic kidney disease, given the doses in question. Finally, the intermediate symptoms Cullen reports are consistent with those in recent cases of AAN. The initial lack of clear symptoms of a specific disease and, crucially, the eventual appearance of progressively worsening edema associated with dropsy resemble the development of renal failure [40].

Nonetheless, Cadogan's and Cullen's published accounts, taken alone, do not provide unequivocal evidence of AAN resulting from the use of birthwort, *per se*. One of the other four ingredients of Portland's Powders, germander, has been associated with acute hepatic toxicity [41]. However, the hepatotoxin in germander, a neoclerodane diterpene, causes symptoms, including jaundice, relatively acutely, making them unlikely to be confused with symptoms attributed to Portland's Powders, which contemporary accounts suggest developed over time. In addition, the unmistakable symptom of jaundice does not appear among the reported symptoms of toxicity from Portland's Powders. Finally, although accumulation of edema attributed to Portland's Powders could result from chronic liver disease, it would be unlikely to arise from acute hepatotoxicity caused by ingestion of germander. Chronic kidney disease is associated with symptoms of dropsy, but so are certain diseases affecting the heart or liver. Cullen's description of progressively worsening "hydropic symptoms" lacks sufficient detail to identify with certainty the underlying cause of these symptoms. Thus far, we are unable to locate any clinical notes or correspondence of Cullen's with additional details concerning the cases in question, but in his *Materia Medica*, he refers the reader to several other works for "illustration and confirmation of all this [38]."

One of these works is a 1758 essay by German physician Hieronymus David Gaubius on the effects of the Duke of Mirandola's gout powder, which, as we have noted, was essentially the same as Portland's Powders. The essay describes the case of an approximately 40-year-old man, healthy other than having mild gout, who took the powder daily for a year and a half [42].<sup>6</sup> According to Gaubius, this man ceased having gout attacks, but starting in the fall of 1756, he suffered from unusual shortness of breath during exercise. This grew progressively worse, prompting him to consult Gaubius in the spring of 1757. Gaubius describes the man as lacking pain and jaundice, but having a dry cough, extreme pallor, a dry and white tongue, and heavily labored breathing when speaking or moving about. He also notes swelling of the man's hands and feet and the area under his eyes, but no swelling of the abdomen. Accompanying these symptoms were unquenchable thirst, abundant and clear urine, and a low pulse rate. None of Gaubius's treatment methods worked, and over the following months, the patient's breathing became more difficult and his strength decreased until, without warning, he died in the night [42].

Gaubius's observations, together with those of Cullen and Cadogan and our estimation of the aristolochic acid content of Portland's Powders, supports the case that ingestion of Portland's Powders, in the doses recommended to treat symptoms of gout, resulted in AAN in 18<sup>th</sup>-century Europe. An additional observation by Gaubius, that the patient needed his head elevated to sleep [42], suggests congestive heart failure, which may have co-existed with renal failure. If Gaubius's patient followed the usual instructions, but stopped treatment after 18 months, he would have ingested approximately 315mg of aristolochic acid, well above the dosage associated with renal toxicity. Even if he followed one of the variant dosage schedules, the total amount of aristolochic acid would not significantly differ. The gradual development of symptoms over many months, without overt pain, is fully consistent with chronic kidney disease. Moreover, in contrast to the common presentation of cardiac diseases, edema caused by renal failure often appears around the eyes, exactly as Gaubius reported [40]. Other symptoms in this case also suggest renal failure. Excessive thirst and abundance of clear urine frequently develop as the kidneys fail and waste products build up in the body. In addition, anemia is regularly associated with kidney disease; this could explain the paleness Gaubius reported in his patient.

## CONTINUING MEDICINAL USE OF ARISTOLOCHIA

By the end of the 18<sup>th</sup> century, Portland's Powders fell out of favor in professional medical circles. Accord-

ing to physician John Scot, writing in 1783, “from a multitude of unfortunate examples this once celebrated remedy entirely lost its reputation and sunk into disuse [43].” He may have overstated matters, but the trend was clear even if at least one respectable pharmacopoeia listed the Portland’s Powders formula as a preventative for gout in 1800 [44]. During the early 19<sup>th</sup> century, the consensus was that Portland’s Powders were “obsolete,” although debates about their safety and effectiveness continued sporadically [45,46]. The 1810 *Family Receipt-Book* (in its third edition by this point), however, gives instructions for the medicine and suggests that it might be beneficial, despite “hav[ing] lost much of it’s [*sic*] celebrity [24].” Still, in 1849, one physician had little to say about the powders, as he had only seen them used once [47].

Despite the powders’ fall, *Aristolochia* herbs remained in European and American pharmacopoeias throughout the 19<sup>th</sup> century, including professionally sanctioned works, such as the *Pharmacopoeia of the United States*, the *British Pharmacopoeia*, and the *London Dispensatory*. These works provide directions for preparing *Aristolochia* for medicinal use, but they fail to mention serious toxicity. This begs the question, why were these recipes still widely available, especially given the widespread attribution of harmful effects to Portland’s Powders, and research on *Aristolochia* in the 19<sup>th</sup> century in humans and animals that clearly revealed the herb’s several toxicities? Likewise, the preceding discussion raises the related question of how Portland’s Powders and similar medicines for gout lasted as long as they did. Both questions shed light on 18<sup>th</sup>- and 19<sup>th</sup>-century medical thinking and are relevant to current issues in public health [13].

A significant part of the answers lies in a combination of factors surrounding the long history of medicinal use of Portland’s Powders and *Aristolochia*. The historical persistence of both could imply their safety; it would be reasonable to conclude that a toxic medicine would have been discarded over the course of the centuries, even if ancient Greek and Roman medical authorities recommended its use. Of course, such a belief ran counter to increasingly critical evaluation of traditional medical authorities, ideas, and practices. Nonetheless, as late as the 1790s, the powders’ history of alternating periods of use and disuse inspired varying and highly contentious conclusions. One “Friend of Improvements” cited cautions “of the ancients” in contending that this history resulted from initial optimism followed by recognition that the powders had “consequences more serious than the gout itself [48].” Physician and Fellow of the Royal Society of Edinburgh, John Gardiner, cited the same ancient cautions and history as evidence of the powders’ efficacy. His piece suggests that the powders have survived so long as a remedy because they work, and that the dangers

apparent both recently and historically arise simply from “injudicious, and indiscriminate use.” The piece thus advances an alternate explanation for the Powders’ rise and fall. Overhype of an effective medicine leads to misuse of the medicine, temporarily destroying its reputation. Indeed, “the mischiefs [*sic*] imputed to these medicines must be considered as a proof of their powers, and that their disgrace was more owing to their having done too much, than their having done too little [23].” Fellow Edinburgh physician Thomas Jeans likewise adduced “from the revival of its [the powder’s] fame at different periods, that some real virtue attached to it.” Portland’s Powders was only dangerous if misused, and if the consequences of misuse were to disqualify a medicine as unsafe, Jeans noted, “we should soon find a great defalcation in the instruments of our art [49].”

Perhaps even more importantly, recognition of the toxicity of *Aristolochia* herbals such as Portland’s Powders was complicated by a lag period of years or even decades between ingestion of aristolochic acid and appearance of symptoms of AAN. Observers were more likely to attribute symptoms of aristolochic acid toxicity to recent events or medications. The apparent safety and effectiveness of *Aristolochia* historically and in contemporary everyday use would add to such a tendency. Moreover, the doses of aristolochic acid in single-use medications containing *Aristolochia*, such as febrifuges and snakebite treatments, would not have had immediately observable deleterious effects. In this, the powders were unusual. Thus, alternate explanations remained plausible long after physicians attributed adverse effects to Portland’s Powders.

Even the few people, like Cullen, who singled out *Aristolochia* as a potential cause for the toxic effects of Portland’s Powders stopped short of arguing for *Aristolochia*’s inherent toxicity, suggesting it could be a safe medicinal herb under the right circumstances. Cullen’s *Materia Medica* describes *Aristolochia*’s daily use in treating gout for extended periods, both in Portland’s Powders and on its own, and ascribes the same negative side effects to both. In support of this assertion, he cites “many instances...recorded by the physicians of Germany,” and quotes one of those physicians, Paul Gottlieb Werlhoff, at length. Werlhoff warns about the dangers of using *Aristolochia* to treat gout, but, like Cullen, avoids stating that *Aristolochia* is dangerous in treating other diseases. Cullen states that he found birthwort (*A. clematitidis*) and Virginia snakeroot (*A. serpentaria*), whose close relation he recognized, medically useful in some instances [38]. In another work, he also temporizes, stating that bitters—a broad class of drugs under which physicians often classed *Aristolochia*—might have use in treating gout, but that one should use them only at the worst time of year for gout, and then for no more than 2 weeks at

a time, with a long break before again using them [39]. Such situation-specific warnings did not make a case for wholly discarding *Aristolochia* from the medicine chest. At least one 1792 work mentions Cullen's warning and states that birthwort had disappeared from the London pharmacopoeia, but plainly, it remained [50].<sup>7</sup> Early modern European medical practitioners and lay healers, like modern practitioners, acknowledged many medicines as useful in certain contexts and dosages, but potentially harmful or even fatal in others, or if taken in large doses or habitually, including drugs such as opium, arsenic, and mercury.

Even if some practitioners favored abandoning *Aristolochia*, the late 18<sup>th</sup>-century medical marketplace lacked significant regulatory mechanisms to enforce such an action. Although the British government played a limited role in curbing the adulteration of foodstuffs during the 18<sup>th</sup>- and early 19<sup>th</sup>-centuries, regulating the safety and sale of medicines was largely beyond its ambit. Statutes dating back to 1540 gave the Royal College of Physicians of London the right to inspect apothecaries' merchandise and to destroy materials they found wanting, rights that only expanded beyond London to the immediate surrounding area and to all people selling medicines in a 1724 law (10 Geo. I c. 20). The latter provision contained significant exemptions, and it lasted only a short time, lapsing in 1731 [51]. The College conducted inspections into the mid-19<sup>th</sup> century, but unsystematically. The 1783 and 1785 Medicine Stamp Duty Acts arguably attempted some indirect government regulation of the market for "quack" medicines, though there was no quality-control and the primary motive was clearly financial [52]. Government regulation of medicines, as opposed to the sale of poisons, in Britain only began in the 1920s, with the Therapeutic Substances Act, and even this law only covered a few drugs [53]. Moreover, the medical profession held no monopoly on medical care during the 18<sup>th</sup> and 19<sup>th</sup> centuries. One could argue that it still does not, given the number of people who treat themselves or adhere to so-called alternative medicines. The potential for the continued use of traditional medicinal use of herbs like *Aristolochia*, therefore, was high regardless of professional medical and toxicological consensus.

## CONCLUSIONS AND OUTLOOK

We argue that AAN is not a new disease but in fact is one that afflicted people long before the era of modern public health, experimental toxicology, and scientific medicine. In this respect, of course, it is hardly unique. Cancer, arthritis, and other chronic diseases also have long histories. What differentiates AAN is that it arises mainly from medical practice and went unrecognized until 25 years ago. Eighteenth-century physicians and

non-physicians alike critically evaluated and publicly debated a range of historical and observational evidence concerning *Aristolochia* and Portland's Powders. Nevertheless, *Aristolochia* continues to be used for medicinal purposes to the present day.

The current state of affairs is similar to the historical situation we have just described. According to the World Health Organization, approximately 80% of people around the world use herbs for disease prevention or treatment [13]. These medicinal herbs comprise a bewildering number of varieties and combinations. The World Health Organization has embraced the notion that a long history of apparently safe use of a medical treatment implies its safety, but the examples of Portland's Powders and modern cases of AAN show clearly that this is not necessarily the case. Various circumstances can mask adverse and even fatal side effects and toxicities, allowing them to continue to cause harm, despite centuries of seemingly safe use. While some herbs, like *Aristolochia*, are intrinsically toxic, others can interact dangerously with prescription medications [54,55]. Further, the preparation and composition of medicinal herbs lack generally accepted standards and are readily subject to contamination or adulteration. Moreover, the recent effective deregulation of herbs marketed as dietary supplements in the United States creates an environment resembling the situation in 18<sup>th</sup>-century Britain. The parallels are alarming. Warnings and bans on products containing *Aristolochia* notwithstanding,<sup>8</sup> over 200 years after recognizing the profound toxicity of Portland's Powders, aristolochic acid-associated nephropathy and urothelial carcinoma continue to threaten the health and well-being of populations throughout the world today [56].

**Acknowledgments:** We thank John Scarborough for translations and keen insights into ancient medical works. A grant from the National Institute of Environmental Health funded costs of our library and analytical research.

## ENDNOTES

<sup>1</sup> Although the earliest references we have found to 'Portland's Powders' date from the early 1750s, the French botanist Joseph Pitton de Tournefort described '*la poudre du Prince de la Mirandole*' [the Prince of Mirandola's powder] in 1698. This composition differed from Portland's Powders by one additional ingredient, and Tournefort's account was translated into English by 1732. Clephane notes the relationship of Portland's Powders and the Duke of Mirandola's Powder, with a 'conjecture' that the latter emerged during the late 15th century.

<sup>2</sup> Based on an estimated 2.04mg of aristolochic acid in each gram of *A. fangchi*.

<sup>3</sup> The Lai 2009 study finds that the danger is associated with cumulative consumption of over 30g of the herb Guan-Mu-Tong and 60g of Guang-Fangchi. Using the above estimate

for *A. fangchi*, this would yield approximately 122mg of aristolochic acid.

- <sup>4</sup> Levels of aristolochic acid in various *Aristolochia* species range between approximately 0.1% and 0.6% dry weight, with the same species varying from season to season. We have used an average figure (0.15%) at the low end of this range for our analysis.
- <sup>5</sup> The phrase “informed speculation” in this context comes from historian Mark Harrison. We agree with Harrison “that if we rule out informed speculation on this subject [identifying and tracking diseases in the past] we would have no way of explaining why diseases appeared, how they spread, or why they disappeared. Despite all the problems inherent in such a task, these questions surely are worth asking.”
- <sup>6</sup> We thank Annette Ricciardi for translating this essay. For an English translation of a summary of the case described in the essay, see Gerard van Swieten, *The Commentaries upon the Aphorisms of Dr. Herman Boerhaave, The late Learned Professor of Physick in the University of Leyden, concerning The Knowledge and Cure of the Several Diseases incident to Human Bodies*, (London, 1765), XIII, 177-8.
- <sup>7</sup> This work states that *A. clematidis*, *A. rotunda*, and *A. longa* were “expunged” from the London Pharmacopoeia’s *Materia Medica*, but that *A. clematidis* remained in that of Edinburgh. Yet it also notes the continued inclusion of *Aristolochia*’s ‘congener’ Virginia Snakeroot (*A. serpentaria*) in both pharmacopoeias.
- <sup>8</sup> A number of countries have banned the sale of herbal remedies containing *Aristolochia*. In 2001, the US Food and Drug Administration banned importation of herbal remedies containing *Aristolochia*, and warned against using such remedies. Although the China Food and Drug Administration issued revised guidelines for medicinal use of *Aristolochia spp.*, it still allows such use.

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