



Research Article

Toxicological Assessment of Apple Seeds: Digestive Transformation of Amygdalin and the Potential Risk of Cyanide Exposure in Humans

Sneha Sinha, Abhishek Kumar Ray, Amit Raj, Sneha Keshari, Badal Kumar Prajapati, Alok Kumar, Ujjwal Kumar, Aman Kumar, Shaesta Firdous, Priyanjali, Vaibhav Singh, Alok Kumar*

Faculty of Medical Science & Research, Sai Nath University, Ranchi, Jharkhand-835219, India.

Apple seeds (*Malus domestica*) contain amygdalin, which is a cyanogenic compound that under the enzyme action can be transformed into hydrogen cyanide (HCN) after the seeds are physically disruption and digested. This paper presents a critique of the botanical source, digestive history, and the toxicity of amygdalin in apple seeds concentrating on an enzymatic pathway that converts a whole glycoside into cyanide in the human gastrointestinal tract. Hydrolytic cleavage mechanism plant β -glucosidase (emulsin) released by breaking or chewing and secondary β -glucosidase producing gut microbes is discussed in parallel with the endogenous detoxification system involving a mitochondrial enzyme rhodanese (thiosulfate cyanide sulfurtransferase). Amygdalin content figures for apple seeds are compiled together with reference doses issued by European Food Safety Authority and the Joint FAO/WHO Expert Committee on Food Additives to make it easier to compare real-life risk levels. Clinical evidence cases from cyanogenic seeds structurally related to the cyanogenic glycosides (apricot kernels) are analysed to show the symptoms and diagnosis pattern of the poisoning of cyanogenic-glycoside since the human case reports of ingestion of apple seeds are very rare. Overall, this summary points out that accidental swallowing of some whole apple seeds is practically a harmless thing for a healthy adult, while deliberately consuming a large amount of crushed or chewed seeds - mostly by a child - might cause an intake of a significant cyanide dose. The article ends with advice on how to limit the risk and also points out limitations of original literature that hinder the development of risk assessments of a specific quantitative level related to apple seeds. Because of the available literature and in reality, cyanogenic poisonings are rare with apple seeds, the conclusion drawn is that it is very unlikely that apple seeds would be a source of poisoning, except when consumed large amounts of the crushed or chewed seeds, mainly by children.

Keywords: Amygdalin, Apple Seeds, Cyanogenic Glycoside, Hydrogen Cyanide, Rhodanese, Cyanide Toxicity, Food Safety.

INTRODUCTION

The apple (*Malus domestica*) is one of the most popular fruits consumed worldwide, and it is not uncommon for people to swallow the apple pips rather than actively removing them. Popular panic over the safety of apple pips, often exacerbated on social media forums, claims that, since they are 'poisonous', otherwise edible apple cores are [1]. While it is true from a chemical perspective that apple pips contain

amygdalin, which is a cyanogenic glycoside that can produce hydrogen cyanide during enzymatic hydrolysis [2], the measure of this fact for the risk to the individual who eats the apple has often not been fully considered. This paper undertakes a specific structured toxicological analysis of apple seed that is formed around three questions. First, on chemical composition, can we determine how much and what

kind of amygdalin exists in an apple seed, and how this varies between cultivars? Second, using the processes of digestion and microbiology what mechanisms are responsible for converting amygdalin into free cyanide in the human gastrointestinal track, and what factors of the host influence these mechanisms? Third, how does the level of cyanide resulting from these mechanisms compare against established toxicological reference doses -acute lethal doses and regulatory reference doses- such that a meaningful, evidence-based risk characterization can be given? Since amygdalin and its subsequent course of digestion are common between several seeds of the Rosaceae family (apples apricots peaches, bitter almonds), and since there are few documented case reports about clinical apple seed in-take, this review relies heavily upon the A lot larger clinical literature for structurally related cyanogenesis from apricot kernels to define the clinical syndrome that can be expected from similar levels of apple-seed consumption, with careful notes on where such extrapolation has been applied.

2. Botanical and Chemical Background

2.1 Amygdalin: Structure, Occurrence, and Historical Context

Amygdalin (D-mandelonitrile- β -D-gentiobioside) is a cyanogenic diglycoside which is constituted of the cyanohydrin mandelonitrile which is linked to the disaccharide gentiobiose [3]. Amygdalin can be found in the seed, kernel and (to a limited degree) in the bark and leaves of a number of Rosaceae including bitter almond apricots peach, cherry and apple [4]. Amygdalin was mainly controversial and related to suspicion due to its use as the clinically unproven cancer cure Laetrile, a purified semi-synthetic representative, promoted from the 1950s on as a cancer cure, despite there being no proven clinical performance and proven cyanide toxicity in the patients receiving it [5]. This is relevant in making a toxicological diagnosis of apple seed because it shows

that cyanide toxicity can be induced in humans with amygdalin by both oral and (less) by intravenous routes of administration in a human clinical setting, speaking to an origin of toxicity in the seed.

2.2 Amygdalin Content of Apple Seeds

Direct measurement for apple seeds has to be done in the most efficient way methodologically, and this was the case in the most recent analytical study from 2015 that was based merely on the identification of amygdalin across 15 apple varieties that can be bought in the stores by way of a technique called high-performance liquid chromatography [6]. They detected that apple seeds contain roughly 1 to 4 milligrams of amygdalin per a gram of seed, a range which was mainly attributable to different cultivars [7]. There were several varieties like e.g. Bramley Coxes, and Jazz which were the ones with highest amygdalin levels, while Braeburn and Egremont Russet were lower ones [8] per the same study commercially available apple juices contain only very minute amounts of amygdalin - about 0.01 to 0.04 mg/ml of freshly pressed juice, and even less - 0.001 to 0.007 mg/ml of long-life pasteurized fruit drinks [9] the fact is that even after crushing the apples, some amount of amygdalin will be released, but this fact alone is quite far from representing an acute danger. For this very reason thermal destruction and settling are the factors that have a significant role in decreasing the amount of the toxin. In addition, since an individual apple seed is in fact the only source being about one-sixth of a gram, it is estimated that one seed will have a tiny fraction of a milligram of amygdalin or, put differently, it will give, with complete hydrolysis of amygdalin, just a small fraction of a milligram of cyanide [10]. Because of this this kind of rough estimate is one that forms the basis for the whole discussion of dose-response in section 5. This type of approximation, the magnitude of a single milligram, is essential as it underlies almost every toxicological discussion.

Table 2.1 — Amygdalin content

Sample / Product	Amygdalin concentration reported	Relative level
Apple seeds	Approximately 1–4 mg/g seed	Highest among listed apple-derived materials
Freshly pressed apple juice	Approximately 0.01–0.04 mg/mL	Lower than intact seeds
Long-life pasteurized apple juice	Approximately 0.001–0.007 mg/mL	Substantially lower
Individual apple seed	Small fraction of a milligram of amygdalin*	Low absolute quantity per seed

3. Digestive Transformation: From Amygdalin to Hydrogen Cyanide

3.1 The Necessity of Cellular Disruption

In a whole apple seed with both parts of the cell membrane intact, amygdalin is sequestered in one compartment while the plant enzyme β -glucosidase (the historical term emulsin has been used for it) responsible for its splitting is located in another [11]. The physical partitioning means that an apple seed which is swallowed whole without being chewed typically goes through the gastrointestinal tract

without significant breakdown of the amygdalin content since gastric acid alone doesn't effectively break the glycosidic bond also there the seed coat that is intact serves as barrier for access [12]. Mechanical disruption - chewing, crushing, or blending, as occurs during juicing - cracks plant cell walls and thereby makes amygdalin available to the endogenous β -glucosidase, and hydrolysis proceeds even before the material is swallowed [13]. This mechanism has been well-documented for apricot kernels where on top of liberation of the enzyme by chewing the toxicity to the ingested cyanogen is increased compared to swallowing a whole kernel [14].

Table 3.1 — Digestive transformation

Stage	Site / source	Major event	Principal product / consequence
1. Mechanical disruption	Mouth / food preparation	Chewing, crushing or blending ruptures seed cells	Amygdalin comes into contact with plant β -glucosidase
2. Initial enzymatic hydrolysis	Seed material / upper GI tract	β -Glucosidase hydrolyses amygdalin	Prunasin + glucose
3. Further hydrolysis	GI tract	Further removal of glucose	Mandelonitrile
4. Cyanide liberation	GI tract	Mandelonitrile undergoes decomposition	Benzaldehyde + hydrogen cyanide
5. Microbial hydrolysis	Intestinal lumen	Gut microbial β -glucosidases act on surviving amygdalin/glycosides	Additional cyanide generation
6. Systemic exposure	After intestinal absorption	Liberated cyanide enters circulation	Potential cyanide toxicity

3.2 Enzymatic Hydrolysis Pathway

The hydrolysis of amygdalin is done step by step. Initially, a β - β -glucosidase removes only one glucose from amygdalin to give prunasin. Then in another hydrolytic step, this second glucose is removed, leading to mandelonitrile. Mandelonitrile is highly unstable and, either on its own, or with the help of an enzyme (mandelonitrile lyase), rapidly breaks down

into benzaldehyde + hydrogen cyanide [15]. This very last step liberates the toxicologically active cyanide ion free of its bound. As the activity of plant β - β -glucosidase enzyme needs cells to be ruptured before it gets access to its substrate, the extent of mastication or mechanical breakdown (processing) is a main factor influencing the level of cyanide that will be generated before or at the time of swallowing [16].

3.3 Gut Microbiota-Mediated Hydrolysis

Another separate hydrolytic way happens after the stomach, right in the bowel. The gut microbes can also hydrolyse the amygdalin that manages to reach them basically intact after mechanical and gastric factors. Gut bacteria, Mainly Bacteroidetes, which are one type of bacteria that are anaerobic, produce many enzymes, including β - β -glucosidase. The presence of this microbiota-dependent pathway gives one plausible explanation to such a event: in controlled experiments where amygdalin is given intravenously without going through the digestive tract, basically no or very little cyanide formation occurs but oral administration regularly yields measurable cyanide release [18]. This difference clearly demonstrates that the gut microbial hydrolysis, not liver or systemic metabolism, is the main source of bioactivation of amygdalin at least when it is swallowed, instead of being injected [19]. The existence of β - β -glucosidase which can hydrolyse phyto glycosides in many other important gut phyla, besides Bacteroidetes, that is, among them are Firmicutes and Actinobacteria, is well established. In some cases, these microbial variations in enzymes at the strain level could be an explanation for the variability in response to cyanogenic glycoside toxicity. [20] All three sections, 3.1 to 3.3, taken individually and together, confirm that the phrase 'digestive transformation', which the article references in the title, actually is, not one

digestive occurrence but a two-part process. First, the plant enzyme hydrolysis is mechanically initiated by the chewing (or processing), and after that, the remnants of amygdalin, which managed to escape the upper gastrointestinal tract and reach the lower intestines, are further hydrolysed by the gut microbiota.

4. Mechanism of Cyanide Toxicity at the Cellular Level

4.1 Inhibition of Cellular Respiration

At the gastrointestinal level, after release of cyanide ion, it is first absorbed and then distributed throughout the body rapidly [21]. Cyanide mainly targets a mitochondrial enzyme, cytochrome c oxidase (or Complex IV of the electron transport chain); cyanide attaches to it with a very high affinity, thereby hindering the last stage of oxidative phosphorylation [22]. With this process of inhibition oxygen-dependent ATP is stopped from being produced and so cells turn to anaerobic respiration instead which creates lactic acid and results in acidosis that typically has a high-anion gap [23]. The heart and brain being the two organs most reliant on a continuous supply of oxidation phosphorylation are the most vulnerable sites for an acute cyanide toxicity and because of this, the clinical manifestations of the poisoning are largely neurological and cardiac [24].

Table 4.1 — Mechanism of cyanide toxicity

Component	Mechanism / Event	Toxicological consequence
Hydrogen cyanide / cyanide ion	Absorbed following liberation from amygdalin	Systemic cyanide exposure
Cytochrome c oxidase (Complex IV)	Cyanide binds to and inhibits the terminal enzyme of the electron transport chain	Inhibition of oxidative phosphorylation
Cellular respiration	Aerobic ATP production is impaired	Cellular energy failure
Anaerobic metabolism	Cells increasingly rely on anaerobic metabolism	Increased lactate production
Acid–base balance	Accumulation of lactic acid	Metabolic acidosis
Brain and heart	High dependence on oxidative phosphorylation	Neurological and cardiovascular manifestations
Rhodanese	Converts cyanide to thiocyanate using a sulfur donor	Endogenous cyanide detoxification
Thiocyanate	Less toxic metabolite subsequently cleared by the kidneys	Reduction of systemic cyanide toxicity

4.2 Clinical Presentation

Signs of poisoning with cyanide in the body that result from ingesting a chemical known as a cyanogenic glycoside can range from mild and gastrointestinal

and neurological symptoms that get cured on their own - like nausea vomiting headache dizziness anxiety - at low levels of exposure, to very severe and potentially life-threatening effects at higher doses, like falling of blood pressure convulsions unconsciousness, coma and in rare cases even death [25]. Symptoms begin quickly; some documented incidents tell of a person being able to eat some kernels of plants capable of producing cyanide and experiencing symptoms from that within just a couple of hours [26]. Besides, symptoms are not very characteristic or very different in appearance because of this a patient presenting with those symptoms can be mistaken to have some other type of gastrointestinal and neurological conditions which often means missed diagnosis. That means, it is only when the medical staff pays close attention and gets inquisitive about the diet of a potential patient that it can lead them to cyanogen poisoning [27].

4.3 Endogenous Detoxification: The Rhodanese Pathway

When it comes to handling small amounts of cyanide, one of humanity's physical defenses is a specific group of enzymes, which work mostly on mitochondrial matrix thiosulfate: cyanide sulfur transferase, a protein commonly referred to as rhodanese [28]. This is a very versatile enzyme rhodanese as it enables the exchange of a sulfur atom from a source, in this case, preferably thiosulfate, to cyanide molecules, thereby turning them into thiocyanate, a compound that has a toxicity two hundred times lesser than the original poison and is mainly taken out by the kidneys [29]. In reality this

detoxification route is the reason why doctors administer sodium thiosulfate (which acts as a cyanide antidote) is a bit of a surprise at first but the logic behind clearly enough, adding sulfur donor substrate to the body increases the speed with which the enzyme neutralizes circulant cyanide in the bloodstream [30]. If a person were to have cyanide only coming from an occasional swallow of a few apple pips at a stretch in their diet, these built-in detox functions usually are considered enough to stop cyanide from building up [31]. That is because when your body makes cyanide from a cyanogon, the amount you get is still less than the rate at which these enzymes remove the cyanide in the body. Clinically toxic concentrations can occur when the rate, or the amount at which, the body is able to release cyanide through the breakdown of various sources exceeds the rate of this detoxification.

5. Dose–Response Considerations and Risk Assessment

5.1 Estimating Cyanide Yield from Apple Seeds

Using the amygdalin level range known for apple seeds and amygdalin hydrogenase stoichiometry, it is estimated that complete hydrolysis of all amygdalin in one apple seed would produce only about a few hundredths of a milligram of hydrogen cyanide (apple seeds contain around 1 to 4 mg amygdalin per gram of seed). Multiplying the average apple core which is said to consist of between 5 to 8 seeds, accidental intake would correspond to a cyanide dosage many magnitudes away from those causing clinical symptoms. [32,33]

Table 5.1 — Dose–response and risk assessment

Parameter	Reported / estimated value	Toxicological significance
Amygdalin concentration in apple seeds	~1–4 mg/g seed	Determines potential cyanide yield
Cyanide yield from a single apple seed	A few hundredths of a mg HCN	Very small absolute cyanide yield per seed
Acute oral lethal dose of cyanide	~0.5–3.5 mg/kg body weight	Broad estimate associated with potentially lethal acute exposure
EFSA acute reference dose	20 µg cyanide/kg body weight	Protective acute dietary reference point
JECFA provisional maximum tolerable daily intake	20 µg cyanide equivalents/kg body weight/day	Reference point for chronic exposure
Estimated number of crushed/chewed apple seeds associated with acute-risk range	~150 to several hundred; potentially higher depending on cultivar	Illustrates large difference between incidental and deliberate exposure

Typical apple core	~5–8 seeds	Represents substantially lower exposure than deliberate large-scale seed consumption
--------------------	------------	--

5.2 Lethal and Reference Doses for Cyanide

The acute oral lethal dose of cyanide in human adults has, through regulatory toxicological assessments, been estimated to range around 0.5 to 3.5 milligrams per kilogram body weight [34], resulting in an approximate lethal dosage of 50 to several hundreds of milligrams in total, which varies according to an individual's sensitivity and the form of exposure [35]. Considering the available data reflecting on the precautionary principle applied in food-safety regulation, the European Food Safety Authority's Panel on Contaminants in the Food Chain fixed an acute reference dose of 20 micrograms of cyanide per kilogram of body weight that they considered as deriving the exposure concentrations corresponding to the non-toxic level of blood cyanide and applying the uncertainty factors tied to interindividual variability [36]. This acute reference dose has later in the follow-up opinion been confirmed as being the exposure level for cyanogenic glycosides from dietary sources generally, and not apricot kernels alone [37]. Concurrently, the Joint FAO/WHO Expert Committee on Food Additives has determined 20 micrograms of cyanide equivalents per kilogram of body weight per day a provisional maximal tolerable daily intake level for chronic exposure to the cyanogenic glycosides which, despite the different derivation approaches [38], is roughly in agreement with the European assessment.

5.3 Translating Reference Doses into Practical Seed Quantities

Using these reference values for apple seeds, published estimates are basically in agreement that an adult would have to eat a fair number of seeds for the cyanide dose to be a risk of acute poisoning. As the articles in the literature, this can be roughly anywhere from 150 to several hundred and some even say a few thousand crushed seeds [39]. As it's very unlikely that we would come across and eat a large number of seeds through regular consumption of apple fruit and since the seeds that are swallowed are mostly passed through the gut as whole, eating apple seeds casually

while consuming the fruit is not a big health risk if one is an adult and in good health [40]. This health risk changes when it comes to scenarios where one would deliberately swallow a large quantity of apple seeds that are ground or blended (e.g. homemade apple juice, smoothies, or preparations of health benefits of seeds), for young children with lower body weight and higher thresholds, and for repeated exposures which in theory lead to a cumulative rather than just acute risk although this has not been clearly explained in papers on the effects of apple seeds.

6. Clinical Evidence from Structurally Analogous Cyanogenic Seeds

Since reports of cyanide poisoning linked to apple seed ingestion in humans well-documented at scientific level are very rare, the authors have decided to base the description on the much larger number of case reports about poisoning resulting from apricot seed ingestion. Apricot seed contain the same cyanogenic compound (*amygdalin*) and share the same pathway via which it gets activated by digestive enzymes. A case report describes a 60-year-old woman who was admitted to emergency department suffering from vomiting, headache and altered consciousness after consuming a large amount of apricot kernels. The woman underwent successful treatment with the cyanide antidote dicobalt edetate following a suspicion of poisoning by cyanide. Still, in this case, cyanide poisoning was arrested, and the patient was saved before cyanide poisoning reached the more deadly stage of toxicity [41]. A pediatric case series describes the poisoning of four children after they consumed apricot seeds in one of which case the children were taken to pediatric intensive care unit and were given a hydroxocobalamin, the recommended antidote that directly binds upide and converts it to the non-toxic compound. The recovery of the children after receiving treatment was very quick [42]. From those two stories, we have got the understanding of two important issues on apple seeds toxicity: one is that poisoning by cyanogenic compounds can be diagnosed correctly even if it is an uncommon scenario, given that there is an appropriate

dietary history; the second one is that among the reported cases children are the most common victims presumably due to in reality the same dose that would be harmless for an adult could be fatal to a child whose body is smaller and that means has a lower dose threshold [43].

7. Modifying Factors Influencing Real-World Risk

7.1 Seed Integrity: Whole Versus Crushed

As shown in Section 3, the physical aspect of the seed when it's ingested is the only major factor that A lot affects cyanide poisoning in general. In whole, undamaged seeds that get swallowed rather than chewed, the enzymatic hydrolysis step can mostly be avoided and the level of poison is relatively smaller. On the contrary crushed blended, or thoroughly chewed seeds expose amygdalin immediately to hydrolytic enzymes, resulting in a marked rise in the cyanide-producing capability that gets translated into free cyanide. [44].

7.2 Food Processing and Thermal Treatment

Studies on commercial juice processing show that through the use of pasteurization and prolonged heating time, the levels of amygdalin are Really reduced compared to freshly pressed juice that still contains crushed seed material. This probably is the consequence of both the thermal degradation of the compound and the partial volatilization of hydrogen cyanide already formed, as hydrogen cyanide has a low boiling point [45]. So, looks like home-prepared, unpasteurized fruit juices or smoothies made by blending together all parts of apples, including seeds and cores, will carry a much higher risk than processed, pasteurized apple products.

7.3 Vulnerable Populations

There are at least two reasons for special caution for younglings: first, from Section 6 some say the case reports pattern has mostly involved young people; second, due to the proportion of child's body weight that a particular amount of poison represents, a much smaller child receives an equivalent dose at a much greater weight per kg than an adult does [46]. The same thing has already been pointed out by dietary exposure evaluations from a public health/regulatory

point of view. For example, babies, young kids, and children are the age groups most exposed acutely and chronically to cyanide if they consume foods that contain cyanogenic glycosides [47]. These results mirror increased relative food intake per kg body weight as well as Truth is some child foods that children commonly consume are the main sources of the total cyanide exposures.

8. Public Health and Regulatory Perspective

The regulatory reference doses described in Section 5 have been mainly related to raw apricot nuts and generally cyanide-glycoside-containing foods, not apple seeds in specific. The apple seed cyanogenic-glycoside (mainly amygdalin) concentration is lower when compared to bitter almonds or apricot kernels because of this this reference was made to apple seeds as well [48]. It is yet necessary to note that the fundamental reasoning, that different dietary cyanide sources of which cyanogenic glycosides are used should be checked against a single reference dose without regard to particular food matrix is a reasoning which has been endorsed explicitly by Contaminants Panel of EFSA [49] and that means the values of reference are directly applicable for risk characterisation of apple seeds despite the absence of a regulatory opinion specific to apple seed. Another concern related to public health is the informal marketing of amygdalin, under names like Laetrile or "vitamin B17, " as a complementary or alternative medicine for cancer [50]. Although amygdalin is a compound that is not chemically active and it lacks biological effects, the compound's ability to release cyanide can bring cyanide poisoning [51]. The use of these products often involves large doses of the substance or a repeated use which is much better than incidental exposure due to fruit consumption and in such situations these users are subject to much more cyanide toxicity risk. Because of this, these users should be in a higher risk situation of cyanide toxicity due to the amount of substance that these products contain compared with the fruit's incidental ingestion dealt with in the other parts of this paper and individuals should not be recommended to self-administer amygdalin-containing preparations, including concentrated apple seed extracts, without a strong medical reason.

9. Recommendations for Risk Mitigation

Based on the evidence, several realistic suggestions can be drawn from what I just said. Removing seeds before letting kids and pets eat apple cores or mixtures of apples is a reasonable precaution, as the reports show a significant difference in frequency between children and other age groups being poisoned from cyanogenic seeds and as well as a Really lower weight-adjusted toxic level in children [52]. The home preparation of apple juice or smoothies should be done by avoiding the combination of seeds and cores in a single batch because the blender physically destroys the seeds triggering the enzymatic reaction unlike incidental swallowing of whole seeds [53]. Pasteurized apple products that are commercially processed have lower chances of poisoning than unpasteurized home preparations, which is in line with the findings of Section 7.2 about the effects of processing [54]. In other words, if you consume concentrated apple-seed preparations, extracts, or Laetrile-type products advertised for imagined health benefits, you should not be doing so, since these preparations are capable of causing cyanamide toxicity, based on the documented potential of concentrated amygdalin exposure [55]. Finally, doctors who are seeing patients with a combination of nonspecific symptoms like metabolic acidosis, confused consciousness, or the cluster of mentioned symptoms should include a food interview with a special focus on the consumption of cyanogenic seed or kernel since the non-specific nature of the symptoms of cyanide poisoning can be a cause for a diagnosis delay [56].

10. Limitations of the Current Evidence Base

Several limitations hinder accurately estimating the risk from this assessment. First, there are hardly any human case reports on cyanide poisoning caused by eating apple seeds. This means that this review relies mainly on information from a much larger database about apricot kernels. The reason is that apricot kernels contain higher concentrations of cyanogenic glucosides, because of this, the symptoms and severity observed in case reports involving apricot kernels cannot be directly used to compare or predict symptoms resulting from an equivalent number of apple seeds [57]. Second, our knowledge of

amygdalin content in apple seeds is based largely on a methodologically sound single systematic analytical study that covered only 15 apple cultivars [58]. The range of concentrations that has been reported might be more reliably extrapolated to the entire apple population and more geographical areas with a broader spectrum of cultivars and a much larger sampling size (if possible). Lastly, our ability to predict a person's cyanide levels based upon their apple-seed intake is currently limited to population risk estimates but it is not an individual precision tool [60] because the factors like the differences of gut microbiota composition and β -glucosidase activity between people have yet to be fully quantified, although they remain under investigation as possible explanatory factors [59].

CONCLUSION

It has been established that apple seeds contain amygdalin, which belongs to the class of cyanogenic glycosides. A two-stage process leads this compound to release highly toxicologically active hydrogen cyanide - the first stage is mechanical disintegration followed by exudation of β -glucosidase enzyme, and the second stage, if amygdalin remains after the first disruption, is the hydrolysis mediated largely by β -glucosidase-producing intestinal microbiota. These mechanisms are very well described in the literature. The effect of cyanide at the biological level is to inhibit the mitochondrial cytochrome c oxidase, an action which is normally counterbalanced by a rhodanese-mediated biotransformation pathway. Given that apple-seed amygdalin levels are compared to established reference doses and estimates of acute lethality for cyanide, the accidental consumption of a few intact seeds via normal fruit eating is hardly a threat to the average adult population health. The risk is entirely different - and should really trigger clinical and public health responses - in cases of planned intake of crushed or blended seeds in large quantities, high-concentration amygdalin preparations and child exposure. With a view to the current dependence for the risk assessment of apple seeds on the closely related but definitely different data on apricot kernels, apparently further apple-seed-specific analytical and clinical studies would result in a greater accuracy of this risk evaluation.

REFERENCES

1. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
2. Encyclopaedia Britannica. (n.d.). Can apple seeds kill you? Cyanide, poison, & facts. Retrieved August 17, 2026, from <https://www.britannica.com/story/can-apple-seeds-kill-you>
3. Jaszczak-Wilke, E., Polkowska, Ż., Koprowski, M., Owsianik, K., Mitchell, A. E., & Bałczewski, P. (2021). Amygdalin: Toxicity, anticancer activity and analytical procedures for its determination in plant seeds. *Molecules*, 26(8), Article 2253. <https://doi.org/10.3390/molecules26082253>
4. Jaszczak-Wilke, E., Polkowska, Ż., Koprowski, M., Owsianik, K., Mitchell, A. E., & Bałczewski, P. (2021). Amygdalin: Toxicity, anticancer activity and analytical procedures for its determination in plant seeds. *Molecules*, 26(8), Article 2253. <https://doi.org/10.3390/molecules26082253>
5. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
6. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
7. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
8. Medical News Today. (2024, February 16). Apple seeds: Are they poisonous? <https://www.medicalnewstoday.com/articles/318706>
9. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
10. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
11. Jaszczak-Wilke, E., Polkowska, Ż., Koprowski, M., Owsianik, K., Mitchell, A. E., & Bałczewski, P. (2021). Amygdalin: Toxicity, anticancer activity and analytical procedures for its determination in plant seeds. *Molecules*, 26(8), Article 2253. <https://doi.org/10.3390/molecules26082253>
12. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
13. Jaszczak-Wilke, E., Polkowska, Ż., Koprowski, M., Owsianik, K., Mitchell, A. E., & Bałczewski, P. (2021). Amygdalin: Toxicity, anticancer activity and analytical procedures for its determination in plant seeds. *Molecules*, 26(8), Article 2253. <https://doi.org/10.3390/molecules26082253>
14. Tatli, M., Eyüpoğlu, G., & Hocagil, H. (2017). Acute cyanide poisoning due to apricot kernel ingestion. *Journal of Acute Disease*, 6(2), 87–88. <https://doi.org/10.12980/jad.6.2017JADWEB-2016-0075>
15. Jaszczak-Wilke, E., Polkowska, Ż., Koprowski, M., Owsianik, K., Mitchell, A. E., & Bałczewski, P. (2021). Amygdalin: Toxicity, anticancer activity and analytical procedures for its determination in plant seeds. *Molecules*, 26(8), Article 2253. <https://doi.org/10.3390/molecules26082253>
16. Tatli, M., Eyüpoğlu, G., & Hocagil, H. (2017). Acute cyanide poisoning due to apricot kernel ingestion. *Journal of Acute Disease*, 6(2), 87–88. <https://doi.org/10.12980/jad.6.2017JADWEB-2016-0075>
17. Jaswal, V., Palanivelu, J., & Ramalingam, C. (2018). Effects of the gut microbiota on amygdalin and its use as an anti-cancer therapy:

- Substantial review on the key components involved in altering dose efficacy and toxicity. *Biochemistry and Biophysics Reports*, 14, 125–132. <https://doi.org/10.1016/j.bbrep.2018.04.008>
18. Jaswal, V., Palanivelu, J., & Ramalingam, C. (2018). Effects of the gut microbiota on amygdalin and its use as an anti-cancer therapy: Substantial review on the key components involved in altering dose efficacy and toxicity. *Biochemistry and Biophysics Reports*, 14, 125–132. <https://doi.org/10.1016/j.bbrep.2018.04.008>
19. Jaswal, V., Palanivelu, J., & Ramalingam, C. (2018). Effects of the gut microbiota on amygdalin and its use as an anti-cancer therapy: Substantial review on the key components involved in altering dose efficacy and toxicity. *Biochemistry and Biophysics Reports*, 14, 125–132. <https://doi.org/10.1016/j.bbrep.2018.04.008>
20. Jaswal, V., Palanivelu, J., & Ramalingam, C. (2018). Effects of the gut microbiota on amygdalin and its use as an anti-cancer therapy: Substantial review on the key components involved in altering dose efficacy and toxicity. *Biochemistry and Biophysics Reports*, 14, 125–132. <https://doi.org/10.1016/j.bbrep.2018.04.008>
21. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2016). Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. *EFSA Journal*, 14(4), Article 4424. <https://doi.org/10.2903/j.efsa.2016.4424>
22. Schaffer, D. H., Poole, N. D., & Traylor, J. (2025). Cyanide toxicity. In StatPearls. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK507796/>
23. Tatli, M., Eyüpoğlu, G., & Hocagil, H. (2017). Acute cyanide poisoning due to apricot kernel ingestion. *Journal of Acute Disease*, 6(2), 87–88. <https://doi.org/10.12980/jad.6.2017JADWEB-2016-0075>
24. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2016). Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. *EFSA Journal*, 14(4), Article 4424. <https://doi.org/10.2903/j.efsa.2016.4424>
25. Schaffer, D. H., Poole, N. D., & Traylor, J. (2025). Cyanide toxicity. In StatPearls. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK507796/>
26. Bıçılıoğlu, Y., Yıldırım, İ., Yazıcı Özkaya, P., & Bal, A. (2020). Pediatric cyanide poisoning after ingestion of apricot seeds. *Journal of Pediatric Emergency and Intensive Care Medicine*, 7(2), 85–88. <https://doi.org/10.4274/cayd.galenos.2019.06977>
27. Schaffer, D. H., Poole, N. D., & Traylor, J. (2025). Cyanide toxicity. In StatPearls. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK507796/>
28. Buonvino, S., Arciero, I., & Melino, S. (2022). Thiosulfate-cyanide sulfurtransferase, a mitochondrial essential enzyme: From cell metabolism to the biotechnological applications. *International Journal of Molecular Sciences*, 23(15), Article 8452. <https://doi.org/10.3390/ijms23158452>
29. Buonvino, S., Arciero, I., & Melino, S. (2022). Thiosulfate-cyanide sulfurtransferase, a mitochondrial essential enzyme: From cell metabolism to the biotechnological applications. *International Journal of Molecular Sciences*, 23(15), Article 8452. <https://doi.org/10.3390/ijms23158452>
30. Buonvino, S., Arciero, I., & Melino, S. (2022). Thiosulfate-cyanide sulfurtransferase, a mitochondrial essential enzyme: From cell metabolism to the biotechnological applications. *International Journal of Molecular Sciences*, 23(15), Article 8452. <https://doi.org/10.3390/ijms23158452>
31. Buonvino, S., Arciero, I., & Melino, S. (2022). Thiosulfate-cyanide sulfurtransferase, a mitochondrial essential enzyme: From cell metabolism to the biotechnological applications. *International Journal of Molecular Sciences*, 23(15), Article 8452. <https://doi.org/10.3390/ijms23158452>
32. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>

33. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
34. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2016). Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. *EFSA Journal*, 14(4), Article 4424. <https://doi.org/10.2903/j.efsa.2016.4424>
35. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
36. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2016). Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. *EFSA Journal*, 14(4), Article 4424. <https://doi.org/10.2903/j.efsa.2016.4424>
37. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2019). Evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels. *EFSA Journal*, 17(4), Article e05662. <https://doi.org/10.2903/j.efsa.2019.5662>
38. Joint FAO/WHO Expert Committee on Food Additives. (n.d.). Cyanogenic glycosides. In WHO Food Additives Series (Chemical evaluation database). World Health Organization. Retrieved August 17, 2026, from <https://apps.who.int/food-additives-contaminants-jecfa-database/Home/Chemical/1086>
39. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
40. Encyclopaedia Britannica. (n.d.). Can apple seeds kill you? Cyanide, poison, & facts. Retrieved August 17, 2026, from <https://www.britannica.com/story/can-apple-seeds-kill-you>
41. Tatli, M., Eyüpoğlu, G., & Hocagil, H. (2017). Acute cyanide poisoning due to apricot kernel ingestion. *Journal of Acute Disease*, 6(2), 87–88. <https://doi.org/10.12980/jad.6.2017JADWEB-2016-0075>
42. Bıcıoğlu, Y., Yıldırım, İ., Yazıcı Özkaya, P., & Bal, A. (2020). Pediatric cyanide poisoning after ingestion of apricot seeds. *Journal of Pediatric Emergency and Intensive Care Medicine*, 7(2), 85–88. <https://doi.org/10.4274/cayd.galenos.2019.06977>
43. Bıcıoğlu, Y., Yıldırım, İ., Yazıcı Özkaya, P., & Bal, A. (2020). Pediatric cyanide poisoning after ingestion of apricot seeds. *Journal of Pediatric Emergency and Intensive Care Medicine*, 7(2), 85–88. <https://doi.org/10.4274/cayd.galenos.2019.06977>
44. Tatli, M., Eyüpoğlu, G., & Hocagil, H. (2017). Acute cyanide poisoning due to apricot kernel ingestion. *Journal of Acute Disease*, 6(2), 87–88. <https://doi.org/10.12980/jad.6.2017JADWEB-2016-0075>
45. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
46. Bıcıoğlu, Y., Yıldırım, İ., Yazıcı Özkaya, P., & Bal, A. (2020). Pediatric cyanide poisoning after ingestion of apricot seeds. *Journal of Pediatric Emergency and Intensive Care Medicine*, 7(2), 85–88. <https://doi.org/10.4274/cayd.galenos.2019.06977>
47. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2019). Evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels. *EFSA Journal*, 17(4), Article e05662. <https://doi.org/10.2903/j.efsa.2019.5662>
48. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2019). Evaluation of the health risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels. *EFSA Journal*, 17(4), Article e05662. <https://doi.org/10.2903/j.efsa.2019.5662>
49. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2019). Evaluation of the health

- risks related to the presence of cyanogenic glycosides in foods other than raw apricot kernels. *EFSA Journal*, 17(4), Article e05662. <https://doi.org/10.2903/j.efsa.2019.5662>
50. Jaszczak-Wilke, E., Polkowska, Ż., Koprowski, M., Owsianik, K., Mitchell, A. E., & Bałczewski, P. (2021). Amygdalin: Toxicity, anticancer activity and analytical procedures for its determination in plant seeds. *Molecules*, 26(8), Article 2253. <https://doi.org/10.3390/molecules26082253>
 51. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
 52. Bıçılıoğlu, Y., Yıldırım, İ., Yazıcı Özkaya, P., & Bal, A. (2020). Pediatric cyanide poisoning after ingestion of apricot seeds. *Journal of Pediatric Emergency and Intensive Care Medicine*, 7(2), 85–88. <https://doi.org/10.4274/cayd.galenos.2019.06977>
 53. Tatli, M., Eyüpoğlu, G., & Hocagil, H. (2017). Acute cyanide poisoning due to apricot kernel ingestion. *Journal of Acute Disease*, 6(2), 87–88. <https://doi.org/10.12980/jad.6.2017JADWEB-2016-0075>
 54. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
 55. Africa Check. (2021, October 22). Apple seeds do contain cyanide-producing amygdalin, but apple seed poisoning extremely unlikely. <https://africacheck.org/fact-checks/meta-programme-fact-checks/apple-seeds-do-contain-cyanide-producing-amygdalin-apple>
 56. Schaffer, D. H., Poole, N. D., & Traylor, J. (2025). Cyanide toxicity. In *StatPearls*. StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK507796/>
 57. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
 58. Bolarinwa, I. F., Orfila, C., & Morgan, M. R. A. (2015). Determination of amygdalin in apple seeds, fresh apples and processed apple juices. *Food Chemistry*, 170, 437–442. <https://doi.org/10.1016/j.foodchem.2014.08.083>
 59. Jaswal, V., Palanivelu, J., & Ramalingam, C. (2018). Effects of the gut microbiota on amygdalin and its use as an anti-cancer therapy: Substantial review on the key components involved in altering dose efficacy and toxicity. *Biochemistry and Biophysics Reports*, 14, 125–132. <https://doi.org/10.1016/j.bbrep.2018.04.008>

Cite: Sneha Sinha, Abhishek Kumar Ray, Amit Raj, Sneha Keshari, Badal Kumar Prajapati, Alok Kumar, Ujjwal Kumar, Aman Kumar, Shaesta Firdous, Priyanjali, Vaibhav Singh, Alok Kumar*, Toxicological Assessment of Apple Seeds: Digestive Transformation of Amygdalin and the Potential Risk of Cyanide Exposure in Humans, *Int. J. Med. Pharm. Sci.*, 2026, 2 (10), 170–181. <https://doi.org/10.5281/zenodo.23168063>