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REVIEW

Amygdalin, quackery or cure?

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ABSTRACT

Background: The cyanogenic diglucoside, amygdalin, has gained high popularity among cancer patients together with, or in place of, conventional therapy. Still, evidence based research on amygdalin is sparse and its benefit controversial.
Purpose: Since so many cancer patients consume amygdalin, and many clinicians administer it without clear knowledge of its mode of action, current knowledge has been summarized and the pros and cons of its use weighed.
Methods: A retrospective analysis was conducted for amygdalin relevant reports using the PubMed database with the main search term “Amygdalin” or “laetrile”, at times combined with “cancer”, “patient”, “cyanide” or “toxic”. We did not exclude any “unwanted” articles. Additionally, internet sources authorized by governmental or national institutions have also been included.
Sections: Individual chapters summarize pharmacokinetics, preclinical and clinical studies and toxicity.
Conclusion: No convincing evidence showing that amygdalin induces rapid, distinct tumor regression in cancer patients, particularly in those with late-stage disease, is apparent. However, there is also no evidence that purified amygdalin, administered in "therapeutic" dosage, causes toxicity. Multiple aspects of amygdalin administration have not yet been adequately explored, making further investigation necessary to evaluate its actual therapeutic potential.

Introduction

The use of complementary and alternative medicine (CAM) has steadily increased over the past decades. CAM includes non-conventional therapy such as homeopathy, vitamin therapy, phytomedicine and traditional Chinese medicine, acupuncture and yoga (Fisher et al. 2014). The ingestion of natural products is the most wide spread CAM practice. Up to 80% of cancer patients in the United States (Saghatchian et al. 2014), and more than 50% of cancer patients in Europe use CAM together with or in place of conventional therapy (Huebner et al. 2014a). Dissatisfaction with conventional treatment and reduction of chemotherapeutic side effects are the most commonly given reasons for using CAM (Gillett et al. 2012; Citrin et al. 2012). Patients also wish to actively contribute to their therapy, hoping to omit no chance of cure (Huebner et al. 2014b).

Information on CAM is mainly obtained from family, friends and increasingly from the internet. These sources are of unknown quality regarding evidence and reliability (Huebner et al. 2014a). Physicians are generally not trained to discuss CAM with their patients (Frenkel et al. 2010) and have little knowledge about CAM themselves (Parker et al. 2013), so that helpful communication between patients and physicians rarely occurs. Reports on the therapeutic efficacy of particular CAM associated compounds are sparse and well-designed, evidence based clinical studies are lacking.

The discrepancy between the use of a natural product and knowledge about a hypothesized anti-tumor property is notably apparent for amygdalin. Amygdalin is a cyanogenic diglucoside (D -mandelonitrile-β- D -gentiobioside; syn: D -mandelonitrile-β- D -glucosido-6-β- D -glucoside) highly concentrated in fruit kernels from *Rosaceae* species such as *Prunus persica* (peach), *Prunus armeniaca* (apricot) and *Prunus amygdalus* var. amara (bitter almond). Amygdalin is naturally found in the dextrorotatory configuration (R-amygdalin), which is considered the active form. The (inactive) S-isomer does not occur naturally (Milazzo et al. 2007). Approximately 50 g/kg (3–5%) amygdalin is found in bitter almond kernels (Lee et al. 2013), between 2.7 and 3.1% in *Semen Persicae* and between 3.6 and 5.2% in *Semen Armeniacae* (Tanaka et al. 2014). In contrast, the amygdalin-content of seeds from apples (*Malus domestica*) range from 1 to 4 g/kg (Bolarinwa et al. 2015).

Proponents of amygdalin consider it a natural cancer cure, based on the unproven theory that amygdalin is specifically broken

Abbreviations: CAM, complementary and alternative medicine; NCI, National Cancer Institute; BfArM, German Federal Institute for Drugs and Medical Devices; i.v., intravenously.

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down to cytotoxic cyanide by the hydrolytic enzyme β-glucosidase, which is supposed to be enriched in tumor cells. It has further been speculated that the mitochondrial enzyme, rhodanese, that detoxifies cyanide by conversion to thiocyanate is not as abundant in tumor cells as in normal cells, leading to selective tumor cell cyanide poisoning. Opponents of amygdalin, however, warn that amygdalin is ineffective and even toxic, since β-glucosidase may not be enriched in tumor cells. Rather, cyanide might systemically accumulate, leading to severe cyanide poisoning.

Since so many cancer patients use amygdalin, and many clinicians administer it without clear knowledge of its mode of action, this overview aims to present current knowledge about amygdalin and discuss the pros and cons of its use.

History of amygdalin

Amygdalin was initially isolated from bitter almonds (*Prunus dulcis*) in the 1830 s by Robiquet and Boutron-Charlard (Wisniak and Robiquet 2013) and further investigated by Liebig and Wöhler. Based on animal as well as self-experimentation by Widtmann and Denk (not clearly described in their publication), amygdalin was designated non-toxic. Liebig and Wöhler concluded that pure amygdalin was vital for general use (Riecke 1840). As early as 1845, amygdalin was used as an anticancer-compound in Russia (Moss 1996). First reports on amygdalin application in the United States date from the 1920 s (Curt 1990). The oral formulation available at that time, however, was judged too toxic and, therefore, abandoned (National Cancer Institute 2015a).

In the 1950 s, a semi-synthetic, injectable form of amygdalin was developed and patented as Laetrile (LAEvorotatory mandeloniTRILE) by Ernst T. Krebs (Dorr and Paxinos 1978). Although the term "laetrile" is frequently used as a synonym for amygdalin, laetrile is structurally different from the natural compound with the chemical composition D -mandelonitrile-β-glucuronide. To avoid confusion, the term amygdalin will be used in the present article. However, the distinction will be made between amygdalin and laetrile, when necessary. Amygdalin became one of the most popular, non-conventional, anti-cancer treatments in the 1970 s and by 1978, 70,000 US cancer patients had used it (Moss 2005). Evaluation of amygdalin produced by a Mexican company revealed that both the oral and injectable forms of amygdalin did not comply with US pharmaceutical product standards, and several ampules were found to be contaminated with bacteria (Davignon et al. 1978). Amygdalin was then banned from transport into the US or across state lines. Nevertheless, use of this substance for terminally ill cancer patients remained legal in 23 states in the USA (Curran 1980).

During this controversial time, the National Cancer Institute (NCI) decided to evaluate the efficacy of amygdalin treatment. A clinical trial, sponsored by the NCI with approval of the US Food and Drug Administration (FDA), failed to demonstrate anticancer activity (Moertel et al. 1982). Since then, amygdalin has been banned by the FDA and not authorized for sale as a medicinal product in the USA or Europe, with some exceptions (Milazzo et al. 2007). In the UK, amygdalin is considered "prescription medicine only" and can only be prescribed under medical supervision (Milazzo et al. 2007). The German Federal Institute for Drugs and Medical Devices (BfArM) has classified amygdalin as a questionable drug (BfArM 2015a). Despite widespread federal limitation, the compound continues to be manufactured and administered as an anticancer drug worldwide. Many websites promote and market amygdalin and many physicians administer it. At least 35 clinics or medical practices in Germany offer an amygdalin based tumor therapy, as shown by an incomplete list compiled by the BfArM (BfArM 2015b). Information is not available about how many persons presently use amygdalin.

Pharmacokinetics

In 1986 Strugala et al. identified two different metabolic pathways for orally administered amygdalin. The first pathway was described as "first pass" metabolism of amygdalin to prunasin (D -mandelonitrile β- D -glucoside) by cleavage of the terminal glucose residue via enzymatic β(1-6)-glucosidase activity in the proximal small intestine. Due to limited analytical methods, earlier studies did not discriminate between amygdalin and prunasin, and tracing amygdalin's metabolic route was not possible. The second pathway was the β-glucosidase driven total hydrolysis of amygdalin to glucose, benzaldehyde and cyanide by microflora in the colon (Strugala et al. 1986) (Fig. 1).

Freese et al. proposed that mammalian β-glucosidase, responsible for the "first-pass" effect, might be different from bacterial β-glucosidase responsible for final hydrolyzation. The reasoning was that human β-glucosidase is primarily localized in the neutral pH cytosol of mammalian tissue, whereas bacterial β-glucosidase is localized in acidic lysosomes (Freese et al. 1980). Corroborating this, reduction of gut flora activity following antibiotic treatment was shown not to influence the hydrolytic cleavage of amygdalin into prunasin, but suppressed total hydrolysis of amygdalin into benzaldehyde and cyanide (Strugala et al. 1986). Still, a preferred metabolic pathway cannot be established since amygdalin degrades to prunasin in both acidic and neutral environments (Strugala et al. 1986). Freese, himself, failed to demonstrate hydrolysis of gentiobiose, the integral part of amygdalin, in mammalian tissue. Several normal and neoplastic tissues have also shown no β-glucosidase activity, which precludes the existence of intracellular β-glucosidase (Newmark et al. 1981) and favors β(1-6) glucosidase localization in humans in the gut wall (Strugala et al. 1986). Other digestive enzymes in the upper gastrointestinal tract that may act like β(1-6) glucosidase have been identified, hydrolyzing amygdalin into glucose and prunasin, as well (Shim and Kwon 2010).

Disregarding enzymatic digestion, experiments in a rat model have shown that prunasin is actively transported in the small intestine by a glucose carrier system, without formation of benzaldehyde or cyanide during passage from mucosa to serosa (Strugala et al. 1995). The carrier system has been identified as the epithelial sodium-dependent monosaccharide transporter SGLT1 (Wagner and Galey 2003). Absorbed prunasin is finally cleared by the kidney without formation of benzaldehyde or cyanide (Rauws et al. 1982). However, isomers of prunasin have been detected by a highly sensitive liquid chromatography-tandem mass spectrometric method (Li et al. 2014), showing that configurational modifications might occur following absorption. Based on a gastrointestinal digestion model combined with a human intestinal cell culture, prunasin has been shown to be degraded into mandelonitrile by β-glucosidase in the small intestine. Prunasin is then taken up as hydroxymandelonitrile into the cells and not further metabolized through mucosal passage (Shim and Kwon 2010). Further investigation is required to prove whether this process takes place in humans or whether it is restricted to an *in vitro* response.

The oral bioavailability of prunasin is 50% and that of amygdalin 1% (evaluated in a hamster model (Frakes et al. 1986)). Apparently, prunasin, a monosaccharide, is specifically transferred, whereas amygdalin, a disaccharide, requires prior hydrolysis by β-glucosidase at the mucosal brush border (Strugala et al. 1986). There is no doubt that β-glucosidase from gut bacteria plays a dominant role in amygdalin metabolism since reduction of gut flora activity following antibiotic treatment drastically decreases hydrolysis of amygdalin into benzaldehyde and cyanide (Strugala et al. 1986). The hydrolytic role of bacteria has been confirmed, since intravenously administered amygdalin does not result in cyanide or benzaldehyde production (Newton et al. 1981). Bacteroides fragilis