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NATURAL PLANT TOXICANT – CYANOGENIC GLYCOSIDE AMYGDALIN: CHARACTERISTIC, METABOLISM AND THE EFFECT ON ANIMAL REPRODUCTION

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Review

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ABSTRACT

The amount of cyanogenic glycosides, as natural plant toxicants, in plants varies with plant species and environmental effects. Cyanogenic glycoside as an amygdalin was detected in apricot kernels, bitter almonds and peach, plum, pear and apple seeds. Amygdalin itself is non-toxic, but its HCN production decomposed by some enzymes is toxic substance. Target of this review was to describe the characteristic, metabolism and possible effects of amygdalin on reproductive processes. Previous studies describe the effects of natural compound amygdalin on female and male reproductive systems focused on process of steroidogenesis, spermatozoa motility and morphological abnormalities of spermatozoa. In accordance to the previous studies on amygdalin its benefit is controversial.

Keywords: Amygdalin, metabolism, reproduction.

INTRODUCTION

Characteristic of cyanogenic glycosides – amygdalin

Cyanogenic glycosides are natural plant toxicants (**Bolarinwa *et al.*, 2015**), HCN-producing phytotoxins. HCN is a powerful and a rapidly acting poison. It is not difficult to find plants containing these compounds in the food supply and/or in medicinal herb collections (**Cho *et al.*, 2013**). There are various forms of cyanogenic compounds that release hydrogen cyanide upon breakdown. The cyanogenic compound is present mainly as glycoside in more than 2650 plant species. Apricot kernel, peach kernel, cassava, almond, bamboo shoot, sorghum, Japanese apricot, flaxseed among others have been consumed by human worldwide either as food or as herbal medicine (**Francisco and Pinotti, 2000**; **Haque and Bradbury, 2002**). About ten cyanogenic glycosides including amygdalin, prunasin, dhurrin, linamarin, and taxiphyllin have been reported in edible plants (**Vetter, 2000**). Amygdalin is one of the nitrilosides, natural cyanide-containing substances abundant in the seeds of plants of the prunasin family (**Chang *et al.*, 2006).** It is a major component of apricot kernels, bitter almonds and peach, plum, pear and apple seeds (**Conn, 1974; Tanyildizi, 1997**). It is widely distributed in plants, especially in the rosaceous plant seed, for example, apricot, peach, cherry, plum etc. (**Holzbecher *et al.*, 1984; Santos Pimenta *et al.*, 2014**). Amygdalin is also called bitter apricot, laetrile, almond; it is a cyanogenic compound and belongs to the aromatic cyanogenic glycoside group. Its molecular formula is: $C_{20}H_{27}NO_{11}$, the molecular weight is 457.42. The chemical structure is D-mandelonitrile-β-D-glucoside-6-β-glucoside. It was one of the most popular, non-conventional, anti-cancer treatments in the 1970s and by 1978, 70,000 US cancer patients had used amygdalin (**Moss, 2005**). Still, evidence based research on amygdalin was and is sparse and its benefit controversial.

Metabolism of cyanogenic glycosides – amygdalin

The amount of cyanogenic glycosides in plants varies with plant species and environmental effects (**Vickery et al., 1987**). For example, apricot seeds and bitter almond contain approximately 20 – 80 μmol/g and 100 μmol/g of amygdalin, respectively (**Conn, 1979**). After oral administration, amygdalin is hydrolysed by rumenal microorganisms and released as benzaldehyde, glucose and cyanide. Both glycosides and released cyanide have toxic effects on animals (**Majak, et al., 1990; Tanyildizi, 1997**). This glycoside is absorbed unmetabolized in the jejunum of the rat via the transport system of glucose to the blood and is then concentrated in the spleen, liver, kidney, stomach and intestines (**Strugala et al., 1995; Adewusi and Oke, 1985**).

The effects of cyanogenic glycosides – amygdalin on reproduction

Amygdalin itself is non-toxic, but its production HCN decomposed by some enzymes is poisonous substance **(Suchard et al., 1998).** Action by endogenous plant enzymes can release hydrogen cyanide causing potential toxicity issues for animals including humans (**Bolarinwa *et al.*, 2015**) including cell death by blocking cytochrome oxidase and the arrest of the ATP production. The acute toxicity experiments of amygdalin have proved that the toxicity of oral administration route is far greater than the intravenous route. The mean lethal dose (LD50) of amygdalin in rats was reported to be 880 mg/kg body weight (BW) by oral administration (**Adewusi and Oke, 1985; Park *et al.*, 2013**). The LD50 of intravenous injection in mice are 25 g/kg, while via intraperitoneal injection is 8 g/kg. The maximum tolerance dose of intravenous and intramuscular injection of amygdalin in mice, rabbits, dogs are 3 g/kg, 0.075 g/kg orally respectively (**Zhang and Jin, 1986; Rauws *et al.*, 1982**) and human intravenous injection are 5 g (approximately 0.07 g/kg).

Female system and amygdalin

Previous studies examined the effects of natural compound amygdalin on female reproductive system concentrated on secretion activity of porcine ovarian granulosa cells (GC) in vitro (**Halenár *et al.*, 2013a**). The release of steroid hormone progesterone by granulosa cells from cyclic and non-cyclic porcine ovaries was not affected by the amygdalin addition (1, 10, 100, 1000, 10 000 μg/mL) (**Halenár *et al.*, 2013a**). But on the other hand, amygdalin (at 10 000 but not at 1, 10, 100, 1000 μg/mL) combined with mycotoxin deoxynivalenol (DON) (1000 ng/mL) significantly ($P \leq 0.05$) stimulated the release of steroid hormones progesterone and estradiol by granulosa cells from non-cyclic porcine ovaries (**Halenár *et al.*, 2013b**). Similarly, release of estradiol by GCs from cyclic porcine ovaries were affected by addition of amygdalin (10, 100, 1000, 10 000 μg/mL) in combination with DON (1000 ng/mL), but not in experimental group with the lowest dose (1 μg/mL) of amygdalin (**Halenár *et al.*, 2013b**).

Male system and amygdalin

The possible impact of different naturally cyanide-containing substances on the male reproductive system, focused on spermatozoa motility and morphological abnormalities in bull spermatozoa, was observed previously (**Tanyildizy and Bozkurt, 2004**). The effects of amygdalin on hyaluronidase activity of spermatozoa, spermatozoa motility and morphology were evaluated in previous study. The treatment of semen samples with amygdalin significantly ($P < 0.01$) inhibited hyaluronidase activity of spermatozoa when compared with the control

group. After the incubation of amygdalin, the spermatozoa motility decreased very significantly (P<0.001) in a dose-dependent manner, and all spermatozoa were immobile at 10 min. In addition, the percentages of morphological abnormalities did not change in comparison with the control group. The control values were between 4.21% and 6.87% (**Tanyildizi and Bozkurt, 2004)**. It is not known whether amygdalin cross the blood-testes barrier. It has been reported that hyaluronidase enzyme plays an important role in supporting spermatozoa penetration into the cumulus oophorus matrix (**Meyers and Rosenberger, 1999**). Hyaluronidase activities were inhibited significantly by amygdalin (P<0.01) (0.4 to 2 μM). The inhibition of spermatozoa hyaluronidase activity and spermatozoa motility showed that these compounds have deleterious effects on bull spermatozoa in vitro (**Tanyildizi and Bozkurt, 2004)**.

On the other hand prostate cancer is one of the most common non-skin cancers in men and amygdalin have been used to treat cancers and relieve pain. In particular, D-amygdalin (D-mandelonitrile-beta-D-gentiobioside) is known to exhibit selective killing effect on cancer cells. Apoptosis, programmed cell death, is an important mechanism in cancer treatment. Human DU145 and LNCaP cells treated with amygdalin exhibited several morphological characteristics of apoptosis. Treatment with amygdalin increased expression of Bax, a pro-apoptotic protein, decreased expression of Bcl-2, an anti-apoptotic protein, and increased caspase-3 enzyme activity in DU145 and LNCaP prostate cancer cells. Amygdalin induces apoptotic cell death in human DU145 and LNCaP prostate cancer cells by caspase-3 activation through down-regulation of Bcl-2 and up-regulation of Bax (**Chang *et al*., 2006**).

CONCLUSION

This review describes the characteristic, metabolism, possible effects of amygdalin on reproductive processes. Amygdalin itself is non-toxic, but HCN production decomposed by some enzymes is toxic substance. The possible effects of natural compound amygdalin on reproduction were shown in previous studies. The mechanism of action of amygdalin is unknown. The toxic effect of amygdalin or its benefit is controversial and realization of in vivo and vitro experiments is necessary.

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