CYANOCENIC GLYCOSIDES AS A POTENTIAL BIOREGULATOR

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ARTICLE INFO

ABSTRACT

Natural substances which are considered to be a food that provides medical and health benefits are called bioregulator. Bioregulators can be used in medicine for preventing and treating migraine, hypertension, chronic inflammation, and other reaction source diseases. Amygdalin is considered for one of the most important bioregulator. It is a controversial nature cyanogenic glycoside abundant in the seeds of Rosaceae family. The family includes herbs, shrubs, and trees and most species are deciduous, but some are evergreen. In the past few years, there has been a renewed interest about distribution of Rosaceae fruits because amygdalin has been used for many years in traditional and alternative medicine. Therefore, it is included in regulatory pathways and processes. Recent data indicate potential regulatory activity of amygdalin in signaling pathways of highly metastatic cells, suggesting that amygdalin might not only be an innovative tool to neutralize metastatic dissemination but also to complement mTOR-inhibitor based regimen.

INTRODUCTION

In recent years considerable effort has been made to identify the metabolic factors linking nutrition with partial physiological processes (Monget and Martin, 1997; Kolesárová et al., 2011). Numerous data from various mammalian species have shown that natural substances may influence the physiological functions (Prunier and Quesnel, 2000) or on the other side tumorigenesis, carcinogenesis, angiogenesis (Subash et al., 2010; Aggarwal et al., 2009). The most widely plant constituents, which are biologically active and provide medical and health benefits are called bioregulators (Brower, 1998; Zeisel, 1999). The function of bioregulators is also important to examine from viewpoint of prevention of many reproductive alterations (Medvedová et al., 2010). Neuroendocrine regulation manages reproductive system through axis hypothalamic, pituitary and gonads (Javorka et al., 2012). Sex hormones (female-estrogens, progesterone, male-androgens: testosterone) are steroids (fat soluble compounds) that control sexual maturity and reproduction. The endocrine glands ovaries, testes, or adrenal cortex regulate sexual development of an organism and affects the growth or function of the reproductive organs. The endocrine and extracellular signalling systems provide a means of communication between distant organs via the circulatory system, specific cell populations, neighbouring cell populations, and the external and internal environments (Chedrese, 2009). Fruits and vegetables contain many different natural compounds, some essential nutrients and also contain a variety of bioactive substances, which have other beneficial health effects (Kris-Etherton et al., 2002). In the past few years, there has been a renewed interest in evaluating the bioregulator content and distribution in patterns of fruits and vegetables (Flood et al., 2002; Ruiz et al., 2006).

Rosaceae family

Family Rosaceae, comprised of over 100 genera and 3000 species, is the third most economically important plant family in temperate regions (Dirlewanger et al., 2002). Rosaceae contain edible members such as almonds, apples, plums, peaches, pears, raspberries, sour cherries, sweet cherries, and strawberries. Other non-edible species with almost exclusively ornamental value include rose, hawthorn, potentilla, cotoneaster, and pyracantha. The products of this family are in high demand for their nutritional and esthetic values edible (Vavilov, 1951). Rosaceae fruits are also a major human dietary source of phytochemicals, such as flavonoids, cyanogenic glycosides, phytoestrogens (Mazur et al., 2000), and phenols that could potentially yield health and disease - fighting advantages. L-

Ascorbic acid, queretin, kaempferol, myricetin, p-coumaric acid, gallic acid, and ellagic acid are well known antioxidants and/or cancer-inhibiting compounds that have been identified in these fruits (Macheix et al., 1991, 1998; Selmar, 1999). The family Rosaceae has found for own rich generic representation of an application in the prevention and treatment of many pathological conditions. In the past few years, has been a renewed interest about distribution of these fruits (Fakuta et al., 2003; Chang et al., 2005). In vitro and in vivo studies on animal models provide evidence that fruit and leaf extracts from many Rosaceae species inhibit some cancers or have strong antioxidant activities (Yau et al., 2002).

Seeds of Rosaceae fruits contain a substantial amount of dietary protein (Nout et al., 1995) along with significant amounts of oil and fiber but this part of apricot also depending on the variety, contain the toxic cyanogenic glycoside - amygdalin (Gomes et al., 1998, Islamiyat et al. (2014) have developed and applied a high performance liquid chromatographic procedure for amygdalin quantification to investigate extraction efficiency and to determine levels in a range of commercially-available foods. Their results showed that seeds from Rosaceae species contained relatively high amounts (range 0.1–17.5 mg/g) of amygdalin compared to seeds from non-Rosaceae species (range 0.01–0.2 mg/g) (Yildirim et al., 2010). The apricot (Prunus armeniaca L.) is a member of the Rosaceae family. Apricot fruit, being a rich source of vitamins and minerals and is one of the most familiar crops worldwide. Their trees are not ubiquitous since they can only grow in certain regions where the environmental conditions are favourable (Baytop et al., 1999). The fresh apricot fruit contains carbohydrates, vitamins C and K, β-carotene, niacin, and thiamine. Organic acids, phenols, volatile compounds, esters, and terpenoids have also been isolated (Ruiz et al., 2006; Riu-Aumatell et al., 2005; Safer et al., 2006).

Bioactive substance - Amygdalin

Natural plant origin products like amygdalin are still a major part of traditional medicine (Iwang et al., 2008). Amygdalin (vitamin B17; previously called laetrile) is one of many nitrosoxides, which are natural cyanide-containing substances abundant in the seeds of prunasin family and other Rosaceous plants (Chang et al., 2005; Pak et al., 1999). The distribution of the cyanogenic glycosides in the plant kingdom is relatively wide and they are present mainly in more than 2650 plant species (Franciscu and Pinotti, 2000; Haque and Bradbury, 2002). There are approximately 25 cyanogenic glycosides which have found in the edible parts of plants being: amygdalin (almonds); dhurrin (sorghum); linamarin (cassava, lima beans); lotaustralin (cassava, lima beans); prunasin (stone fruit); and taxiphyllin (bamboo shoots) (Gonzales and Sabatini,
1989). Cyanide is a toxic substance, mainly due to its affinity for the terminal cytochrome oxidase in the mitochondrial respiratory pathway (Brattsten et al., 1983). The lethal dose of cyanide for vertebrates lies in the range of 35–150 μmol/kg, if applied in a single dose. Much higher amounts of HCN can be tolerated if consumed or administered over a longer period (Davis and Nahrstedt, 1985). Biosynthesis and degradation of cytagenic glycosides (CNGs) are well documented in many plants (Jones et al., 2000; Lechtenberg and Nahrstedt, 1999).

But the genetic control of cyanogenesis has no unique mechanism, the plants show variation in the amount of the produced CNGC. The production of HCN depends on both the biosynthesis of CNGS and on the existence (or absence) of its degrading enzymes. The biosynthetic precursors of the CNGs are different L-amino acids, these are hydroxylated then the N-hydroxyamino acids are converted to aldoximes, these are turned into nitriles. The last ones are hydroxylated from α-hydroxynitriles and then are glycylated to CNGS. The generation of HCN from CNGs is a two steps process involving a deglycosylation and a cleavage of the molecule (regulated by β-glucosidase and α-hydroxynitrilase). The tissue level compartmentalisation of CNGs and their hydrolysing enzymes prevents large-scale hydrolysis in intact plant tissue. The actual level of CNGS is examined by various factors both developmental and ecological ones, which are reviewed too (Vetter, 2000).

Amygdalin is composed of two molecules of glucose, one of benzaldehyde, which induces an analgesic action, and one of hydrocyanic acid, which is an anti-neoplastic compound (Zhou et al., 2012).

Figure 1 Chemical structure of amygdalin (Abdel-Rahman, 2011). Action of endogenous plant enzymes can release hydrogen cyanide causing potential toxicity issues for animals and humans, including cell death by blocking cytochrome oxidase and the arrest of the ATP production (Bolarinwa et al., 2014). Amygdalin has been used to treat cancers and relieve pain (Ellison et al., 1978; Shim et al., 2000). Amygdalin was reported to selectively kill cancer cells at the tumor site without systemic toxicity and to effectively relieve pain in cancer patients (Zhou et al., 2012). The acute toxicity experiments of amygdalin have proved that the toxicity of oral administration route is far greater than the intravenous route (Adewusi and Oke, 1985; Park et al., 2013). The maximum tolerance dose of intravenous and intramuscular injection of amygdalin in mice, rabbits, dogs are 3g/kg, 0.075 g/kg orally respectively (Zhang and Jin, 1986; Rauws et al., 1982) and human intravenous injection are 5g (approximately 0.07 g/kg). Previous studies on amygdalin have focused on its purification, toxicity related to the release of cyanide, anti-tumor mechanism, and identification of its metabolites in plasma or herbs, and its pharmacological effect on cancers. Rauws et al., 1982, Song and Xu, 2014). Recent studies examined the effects of natural compound amygdalin on female reproductive system concentrated on secretory activity of porcine ovarian granulosa cells (GC) in vitro (Halenár et al., 2013a). Halenár et al. (2015) have the investigated release of steroid hormone progesterone by GC from cyclic and non-cyclic porcine ovaries. The progesterone release was not significantly (P>0.05) affected by the amygdalin treatment at all experimental doses (1, 10, 100 and 1000 μg/ml) compared to the control group without addition. However, a significant stimulation (P<0.05) of the 17β-estradiol release after amygdalin addition at the highest dose (10000 μg/ml) was observed. Other experimental doses of amygdalin (1, 10, 100 and 1000 μg/ml) did not cause differences in the 17β-estradiol secretion. Kolesár et al., (2015) in their review have described the characteristic, metabolism and possible effects of amygdalin on reproductive processes. Previous studies described the effects of natural compound amygdalin on female and male reproductive systems focused on process of steroidogenesis (Halenár et al., 2013a, 2015), spermatogenesis mutility and morphological abnormalities of bull spermatozoa (Tanyildiz and Bozkurt, 2004). Amygdalin significantly inhibited sperm hyaluronidase activity. The inhibition of hyaluronidase activity can cause a drop in the fertilization ability of bull spermatozoa due to the prevention of acrosomal reaction. However, amygdalin did not produce any morphological abnormality in bull spermatozoa. The inhibition of sperm hyaluronidase activity and spermatozoa motility showed that these compounds have deleterious effects on bull sperm in vitro (Tanyildiz and Bozkurt, 2004).

Amygdalin is one of main pharmacological components of crude ingredients of Keishi-bukaryo-gan, Japanese herbal medicine (Yasui et al., 2003). It has been used for induction of ovulation in women suffering from infertility (Igarashi, 1988). Keishi-bukaryo-gan and its crude ingredients affected steroidogenesis in pre-ovulatory follicles (Usuki, 1987, 1990, 1991) and the corpus luteum (Usuki, 1986, 1988) in the rat ovary in vivo and in vitro.

The characterization and role of mTOR Mammalian target of rapamycin (mTOR) is a serine/threonine kinase, which belongs to the phosphatidylinositol-3 kinase (PI3K) family. It regulates cellular metabolism, growth, proliferation, and therefore is a target for the development of a number of mTOR inhibitors (Poppulo et al., 2012). Akt functions as a component of the PI3K cell survival pathway. In cancer, Akt activity is frequently elevated due to multiple mechanisms, including loss of function of the PTEN tumor-suppressor gene and mutations of the PI3KCA gene. Akt functions as a component of the PI3K cell survival pathway (Manning et al., 2005). Akt acts as a survival kinase in many cancers (Cheng et al., 2005). The PI3K pathway is implicated in cell survival and cell growth, and can be activated by growth factors binding to cell-surface receptors. It is an intracellular signaling cascade that is among the most frequently activated pathways in different types of cancer. PI3K is the subject of extensive research (Knight et al., 2007).

Qian et al. (2015) submitted a study where Western blot results showed that amygdalin had no significant impact on Akt and Rictor expression. Rictor as a subunit of mTOR plays an important role in the Akt-mTOR signaling pathway; its phosphorylation level is positively regulated by Akt (Chen et al., 2010). But the determination of Akt and rictor phosphorylation level showed that amygdalin significantly reduced the phosphorylation level of these two proteins in highly metastatic cells, suggesting that amygdalin was able to regulate the activity of Akt and rictor signaling pathways (Qian et al., 2015). The PI3K pathway is a key signal transduction pathway that links oncogenes and multiple receptor classes to many essential cellular functions, and is perhaps the most commonly activated signaling pathway in human cancer. This pathway therefore presents both an opportunity and a challenge for cancer therapy. Even as inhibitors of targeted PI3K isoforms and other major nodes in the pathway, including Akt and mTOR, reach clinical trials, major issues remain. Liu et al. (2009) describe the progress made in understanding of the PI3K pathway and discuss the potential of and challenges for the development of natural therapeutic agents that target this pathway in cancer. Liu et al. (2009). Thus, amygdalin might not only be an innovative tool to neutralize metastatic dissemination but also to complement mTOR-inhibitor based regimens (Gupta et al., 2013).

SUMMARY, CONCLUSIONS, AND FUTURE PERSPECTIVES This review described possible effects of natural bioregulators on various types of animal cells. In recent years, increasing attention has been paid to natural substances and their impact on specific pathways in the cell. Amygdalin, as natural product shows lot of evidences. This natural compound is known for its anticancer, anti-inflammatory activity and other medicinal benefits, but on the other hand it represents a potential source of endogenous plant enzymes. Although amygdalin itself is non-toxic but its production HCN splitted by some endogenous plant enzymes is toxic substance for animals including humans. These agents that inhibit the downstream protein kinase mTOR as well as agents that inhibit multiple kinases, including components of the PI3K-Akt pathway are under clinical evaluation. There are still only a few studies which could suggest the possible involvement of amygdalin in mTOR pathway and thus influence animal reproductive system. Therefore other in vitro and in vivo experiments are necessary.

Acknowledgments: This work was financially supported by the Ministry of Education, Science, Research and Sport of the Slovak Republic projects no. I/0039/16, KEGA 011SPU-4/2016, Slovak Research and Development Agency, APVV-0304-12, and European Community under project no 2622020180: Building Research Centre „AgroBioTech“.


Baytop T. Türiyekle bıktırılar tedavi. İstanbul: İstanbul Eczacılık Fakültesi Yayınları; 1999. http://dx.doi.org/10.1510/jifhaf.000001385


http://dx.doi.org/10.1080/03601234.2015.1011956


