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Attenuation of cellular oxidative stress by natural products and plant extracts after chemotherapeutic exposure

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ABSTRACT

Some natural foods are proved to be useful in prevention of the side effects, caused by the chemotherapeutic agents, both *in vitro* and *in vivo*. Many of the compounds, containing in them, are also approved as potent anti-malignacy agents. As one of the main mechanisms of the action of anti-oxidant molecules is by protection against chemically-induces oxidative stress, by cascade mechanisms, involving modification of autophagy and apoptosis. Also, the role of regulatory pathways, underlining the differentiation of immune cells and immune system, is proved. In this way, the combination treatment with both chemotherapeutic agent plus natural product(s), is proposed to allow a stronger toxicity to malignant cells, rather than to reduce the side effects. Among the main molecules in these processes, is established the reduced form of tri-peptide glutathione (GSH), glutathione-S-transferase (GST), superoxide dismutase (SOD), catalase (CAT) and beta-galactosidase. The mechanisms of cell protection probably involve the reduction of intra-cellular oxidative stress, maintaining GSH availability, but also increased expression and activity of GST enzyme.

Key words: natural products, chemotherapeutic agents, antioxidants

Introduction

Some natural foods as soy, sesame, tomato, grapes, garlic, tomato, spinach, known to contain antioxidant substances as polyphenols, selenium, flavonoids, anthocyanins, proanthocyanidines, L-carnitine, Omega-3 fatty acids, and coenzyme Q10 (CoQ10), have been proved as useful in prevention of cardiotoxicity, induced by Doxorubicin and/or other chemo-therapeutic agents (Dudka et al., 2012; Kähkönen et al., 1999; Lou et al., 2004; Manach et al., 2005; Minotti et al., 2004; Oliveira et al., 2004; Park et al., 2003; Shad et al., 2007; Shahrari & Abdolkarimi, 2014; Zdunczyk et al., 2002; Zhang et al., 2009) (Table 1). Because of the wide spectrum of side effects on the influence of the anti-malignancy agents, many components, isolated from plants have been proved to neutralize them by various intra-molecular mechanisms, by enhancing of the usable influence at the same time (Hafidh et al., 2009). These foods and substances, have been shown to neutralize negative side effects, caused by Doxorubicin (Alexieva et al, 2010; Injac & Strukelj, 2008; Kähkönen et al., 1999; Kong et al., 2003; Pavlova et al., 2014; Sainova et al., 2012; Sainova et al., 2014; Sainova et al., 2015; Wang & Stoner, 2008; Wang et al., 2012; Zdunczyk et al., 2002; Zhang et al., 2009). Similar neutralizing influence on the side toxic effects, induced by other chemotherapeutic drugs (Daunorubicin, Epirubicin, Idarubicin), have been shown by the same natural foods and anti-oxidant molecules, but also by vitamins A, C and E, Resveratrol and olive oil (Alexieva et al, 2010; Das & Poudel, 2006; Granados-Principal et al., 2010; Han et al., 2008; Han et al., 2012; Quiles et al., 2002). As other natural products, found to increase significantly the cardiac cell survival from Doxorubicin-induced toxicity, has been characterized the extract from *Pummelo* (*Citrus maxima*)

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(Chularojmontri et al., 2013). Several different mechanisms of anti-malignant and protective effects of those biologically-active substances against the chemical drug injuries, have been established: neutralization of the free radicals, influence of intra- and extra-cellular inter-molecular cascade regulatory pathways, immune-modulation, but also different combinations between them, subsequently enhancing their therapeutic activity. Also, over-lapping between the different mechanisms of protection and neutralization could be established.

Enhanced anti-malignant activity in combination of Chemotherapeutics with natural products and plant extracts

Combination treatment with Doxorubicin and HO-3867 has been found as able to allow a strong toxicity to breast cancer cells, rather than to reduce the cardiac side effects (Dayton et al., 2011) (Table 1). Because of the high content of polyphenols and anthocyanins, the medical plant *Aronia melanocarpa* (*Chokeberry*) has been applied as a strong anti-cancer and chemo-protective agent (Alexieva et al., 2014; Kähkönen et al., 1999; Kong et al., 2003; McDonnald et al., 1997; Pavlova et al., 2014; Sainova et al., 2012; Sainova et al., 2014; Sainova et al., 2015; Wang & Stoner, 2008; Wang et al., 2012; Zapolska-Downar et al., 2012; Zdunczyk et al., 2002). In XX century, this plant has become popular in many countries all over the world not only with its valuable food qualities, but also as a therapeutic and prophylactic supplement (Domarew et al., 2002; Han et al., 2008; Han et al., 2012; Hovmaln Persson et al., 2004; Kokotkiewicz et al., 2010). As a rich source of polyphenols and anthocyanins, the extract of this plant has been applied as a natural anti-hypertensive and anti-atherosclerotic drug (Domarew et al., 2002; McDonnald et al., 1997), but also as anti-cancer, antioxidant and chemo-protective agent (Kong et al., 2003; Stoner et al., 2008; Wang & Stoner, 2008; Zdunczyk et al., 2002). In a recent study, protective action of *Chokeberry* extract against oxidative stress, induced by high doses of glucose in pancreatic cells has been shown *in vitro* and *in vivo* (Kujawska et al., 2011; Rugina et al., 2011). According the results from another investigation, combination of Doxorubicin treatment with the isolated from the plant *Polygonum multiforum* substance tetrahydroxystilbene glucoside (THSG) has been suggested as a promising anti-malignancy strategy by enhancing the anti-malignancy action *in vitro* and *in vivo* (Zhang et al., 2009). Similar clinical efficiency *in vivo* has been established in combination of Doxorubicin with Taurine in laboratory mice with experimentally-induced tumors (Sadzuka et al., 2009) and substance HO-3867 (Dayton et al., 2011). On the other hand, preventive influence of many natural substances as proanthocyanidines against the induced by Doxorubicin and other chemo-therapeutic drugs mutagenic effects have been indicated (Attia et al., 2010). Additionaly, activation of immunological mechanisms (including anti-malignant) has been indicated *in vitro* and *in vivo* (El-Benna et al., 1986; Huang & Terstappen, 1994; McDonnald et al., 1997; Sainova et al., 2012; Sainova et al., 2014; Sainova et al., 2015; Zapolska-Downar et al., 2012; Zielinska-Przyjemska et al., 2007).

Cardio-protective effects of natural products and plant extracts

Different influences of Resveratrol on the oxidative stress and cardiac morphology have been found, depending of its dose (Dudka et al., 2012). Hence, this substance probably modulates the hepatic and cardiac effect of Doxorubicin, depending on the drug dose (Pavlova et al., 2014), both *in vitro* and *in vivo* (Sainova et al., 2012; Sainova et al., 2014; Sainova et al., 2015; Zhang et al., 2009). These compounds have also indicated various mechanisms of enhanced anti-malignacy effects in their combined use with chemo-therapeutic agents, both *in vitro* and *in vivo* (Alexieva et al., 2010; Hafidh et al., 2009; Scott et al., 2011) (Table 1). As other substances, which have shown cardioprotective effects against the Doxorubicin-induced toxic negative effects, have been proved alpha-Lipoic acid (Mohamed et al., 2010), Taurine (Sadzuka et al., 2009), Aminoguaninidine (Cigremis et al., 2005), Melatonin (Liu et al., 2002; Oz et al., 2006), N-acetylcysteine and selenium (Park et al., 2003), but also the isoquinoline alkaloid Berberine (Zhao et al., 2011). According to the data from another study, the natural compound Curcumin has been found to protect the heart from the Doxorubicin-induced cardiotoxicity by suppression of cardiomyocytes apoptosis, but induction of their autophagy by regulation of JNK-phosphorylation (Katamura et al., 2014). In this way, Curcumin has been shown to protect the cardiomyocytes from the Doxorubicin-induced apoptosis. Similar against apoptosis and necrosis, caused by Doxorubicin, has shown the hormone Melatonin (Liu et al., 2002) and *Pummelo* extract (Chularojmontri et al., 2013). According to another investigation, the role of Aminoguanidine against Doxorubicin-related cardiomyopahy has been indicated (Cigremis et al., 2005). Pre-treatment with natural products and plant extracts has been found to increase

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the endogenous anti-oxidant molecules SOD, GSH and catalase (CAT) in mouse and rat *in vivo*-models, but also in *in vitro*-cultivated normal and malignant cells from human H9C2 cell line and A594 cancer line (Han et al., 2008; Han et al., 2012; Wang et al., 2012). Similarly, the levels of GSH have been established to be decreased in heart tissue from the same animals, treated with Doxorubicin (Pavlova et al., 2014; Wang et al., 2012). Other molecules, possessing protective effect against Doxorubicin-induced cardiotoxicity, are Cystathionine both *in vitro* and *in vivo* (Kwiechen et al., 2006) as well as Naringenin and its derivatives (Attia et al., 2010; Han et al., 2008; Han et al., 2012). Here again, a protective effect of these natural substances against the induced by Doxorubicin oxidative damages on the cardionmyocytes has been shown. However, no interference of this substance with the Doxorubicin antitumor effect was established (Kulling & Rawel, 2008; Lou et al., 2004). On the other hand, the protective action of molecule Tetrahydrostilbene glucoside (THSG) against the Doxorubicin-induced toxic effects *in vitro* and *in vivo*, has been found to be by decreasing of ROS generation and intra-cellular Ca^{2+}, as well as by inhibition of apoptotic signaling pathways (Rugina et al., 2011; Zhang et al., 2009). On the other hand, the aerobic exercise has been suggested as one of the non-pharmacologic therapeutic strategies, which promise to attenuate Doxorubicin-induced cardiotoxicity (Alexieva et al., 2014; Pavlova et al., 2014; Sadzuka et al., 2009). Extract from *Aronia melanocarpa* has become popular as a therapeutic and prophylactic supplement, but also as a natural anti-hypertensive and anti-atherosclerotic drug (Alexieva et al., 2014; Denev et al., 2012; Kähkönen et al., 1999; Kong et al., 2003; Kujawska et al., 2011; Wang & Stoner, 2008; Zapolska-Downar et al., 2012; Zhao et al., 2011). Similar cardio-protective effects against the chemo-therapeutic agents have been established about the garlic and its extracts (Das & Poudel, 2006), but also about the olive oil (Granados-Principal et al., 2010) and sesame oil (Shad et al., 2007). Analogically, N-acetylcystein and selenium (Park et al., 2003), Aminoguanidine (Cigremis et sl., 2005), alpha-Lipoic acid (Mohamed et al., 2010) and compound HO-3867 have also been proved to protect the cardio-vascular system against the negative drug action. Participation of the mitochondria has been proposed in the As a main mechanism of both Doxorubicin-induced cardiotoxicity is established the mitochondria injury on the influence of the drug (Oliveira et al., 2004). The same authors have shown the importance of these cell organelles in the preventive action on the natural products.

Immuno-modulation influence of natural products and plant extracts

Influence of *Aronia melanocarpa* ingredients on the neutrophil differentiation have been established (El-Benna et al., 1986; Huang & Terstappen, 1994; McDonnald et al., 1997; Sainova et al., 2012; Sainova et al., 2014; Sainova et al., 2015; Zapolska-Downar et al., 2012; Zielinska-Przyjemska et al., 2007). Intra-cellular anti-oxidant mechanisms have also been proposed as underlying in the immuno-modulatory influence of the plant ingredients, both *in vitro* and *in vivo* (El-Benna et al., 1986; McDonnald et al., 1997; Sainova et al., 2014; Zapolska-Downar et al., 2012; Zielinska-Przyjemska et al., 2007) (Table 1).

Main molecules and intra-molecular interactions, underlining the protective effects of natural products and plant extracts

As one of the main mechanisms of the action of antioxidant molecules has been characterized the protective influence against the chemically-induced oxidative stress (Attia et al., 2010; Hafidh et al., 2009; Han et al., 2012; Kokotkiewicz et al., 2010). In this way, a protective action of the extract from *Pummelo* has been found to protect the Doxorubicin-induced oxidative stress (Chularojmontri et al., 2013). Also, cascade mechanisms, underlining the differentiation of immune cells and immune system, have been proved (Jahngen-Hodge et al., 1997; Kong et al., 2003; Zhu et al., 2012) (Table 1). As main molecules, included in these processes, have been established the reduced form of tri-peptide Glutathione, particularly its reduced form (GSH) (Sainova et al., 2014) but also enzymes participating in its metabolism as Glutathione-transferase (GST) and beta-galactosidase (Oliveira et al., 2004). The mechanisms of cell protection have been found to involve the reduction of intra-cellular oxidative stress, maintaining GSH availability, but also increased expression and activity of GST enzyme (Chularojmontri et al., 2013). Furthermore, in long-term treatment with this plant extract, suppression of the Doxorubicin-induced cellular senescence has been established, and as one of the main molecules in the mechanisms, underlining this process, has been characterized the enzyme iso-form ESTP, known to be important about the elimination of toxic substances.

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Table 1. *Different mechanisms of chemo-protective influence of natural sources and their components*

	Cell cultivation studies	**Animal studies**	**Human studies**
Cardio-protective effects of natural products and sources from them	- by influence on the levels of free radicals (Chularojmontri et al., 2013; Han et al., 2008; Zhang et al., 2009) - by influence on cascade regulatory pathways (Chularojmontri et al., 2013; Dayton et al., 2011; Han et al., 2008; Han et al., 2012; Wang et al., 2012; Zhang et al., 2009) - by anti-inflammatory activity (Zapolska-Downar et al., 2012)	- by influence on cascade regulatory mechanisms (Cigremis et al., 2005; Katamura et al., 2014; Kwiechen et al., 2006; Liu et al., 2002; Mohamed et al., 2010; Oliveira et al., 2004; Oz et al., 2006; Park et al., 2003; Shad et al., 2007; Wang et al., 2012; Zhang et al., 2009; Zhao et al., 2011) - by decrease of the oxidative stress (Arafa et al., 2005; Kujawska et al., 2011; Mohamed et al., 2010; Oliveira et al., 2004; Park et al., 2003; Shad et al., 2007; Zhang et al., 2009)	- by decrease of the oxidative stress (Das & Poudel, 2006; Granados-Principal et al., 2010; Manach et al., 2005; Quiles et al., 2002) - by influence on cascade regulatory mechanisms (Manach et al., 2005; Scott et al., 2011)
Enhancing the chemotherapeutic anti-malignant effects	- by influence on the levels of free radicals (Wang & Stoner, 2008) - by influence on cascade regulatory pathways (Wang & Stoner, 2008) - by immune-modulation (El-Benna et al., 1986; Kokotkiewicz et al., 2010; Zapolska-Downar et al., 2012; Zielinska-Przyjemska et al., 2007)	- by influence on cascade regulatory pathways (Sadzuka et al., 2009; Wang & Stoner, 2008) - by decrease of the oxidative stress (Attia et al., 2010; Kwiechen et al., 2006; Ortega et al., 2011; Wang & Stoner, 2008) - by immune-modulation (Kong et al., 2003; Wang & Stoner, 2008)	- by influence on cascade regulatory pathways (Wang & Stoner, 2008) - by decrease of the oxidative stress (Hafidh et al., 2009; Injac & Strukelj, 2008; Kokotkiewicz et al., 2010; Kulling & Rawel, 2008; Wang & Stoner, 2008)
Other usable effects	- stimulation of normal immune cell differentiation (El-Benna et al., 1986; Rugina et al., 2011; Sainova et al., 2012; Sainova et al., 2014; Sainova et al., 2015; Zapolska-Downar et al., 2012; Zielinska-Przyjemska et al., 2007)	- gastro- and hepato-protective influence (Dudka et al., 2012; Pavlova et al., 2014; Rugina et al., 2011)	- hepato-protective, gastro-protective, neuro-protective, anti-diabetic, anti-bacterial, anti-viral, anti-inflammatory effects (Kokotkiewicz et al., 2010; Ortega et al., 2011; Wang & Stoner, 2008)

These results indicated a strong scavenging effect of chokeberry anthocyanins on the intracellular reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Alexieva et al., 2010). The mechanism of Aminoguanidine protective action against Doxorubicin-induced side effects has been proved to be mainly by the role of this nature compound as a free radicals scavenger (Cigremis et al., 2005). Ability to restore dose-dependently the strong decrease of the levels of the intracellular reduced GSH has been established (Ortega et al., 2011). According to other data, anthocyanin-mediated increase of GSH synthesis and protection of hepatocytes against ROS–induced injury has been proposed (Lou et al.,

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2004; Zhu et al., 2012). Analogical mechanisms have been established in the prevention of Adriamycin side effects by anti-oxidant nutrients (Principal et al., 2010). GSH deficit has been found to disrupt the redox-status and upsets the physiological cellular balance between pro-oxidants and antioxidants (Injac & Strukelj, 2008). Lowered cellular GSH has been observed in different pathological conditions (pre-malignancies and malignancies, inflammations, Parkinson's disease, Acquired Immuno-Deficiency Syndrome (AIDS) and other immune pathologies, diabetes, etc.) (Ortega et al., 2011). Thus, GSH modulation could represent a supportive measure to achieve a therapeutic goal.

Conclusion

Because of the high content of anti-oxidant substances, many natural foods are useful in the prevention of side effects of chemotherapeutic drugs. Also, many of those molecules are proved as anti-malignancy and immuno-modulation enhancers. As one of the main mechanisms of this action is proved their action against the chemically-induces oxidative stress, by cascade pathways, with participation of internal anti-oxidant molecules as GSH, GST, SOD, CAT and beta-galactosidase. Over-lapping between different mechanisms of cardio-toxic, anti-malignancy and other protective effects in the three types of biological systems tested could very often be noted. This might be explained with manifestation of the protective effects of the natural products as result of action of several different mechanisms, but also with resulting and interaction between each other or between different components from them.

References

Alexieva B, Markova Tz, Nikolova E, Aragane Y, Higashino H. 2010. Free radicals, antioxidants and cancer chemotherapy. Acta Med. Kinki Univ., 35(2): 57-65.

Alexieva B, Sainova I, Pavlova V, Markova Tz, Valkova I, Nikolova E. 2014. Insights into mechanisms of Doxorubicin toxicity. J. Physiol. Pharmacol. Adv., 4(3): 342-348.

Arafa HM, Abd-Ellah MF, Hafez HF. 2005. Abatement of Naringenin of Doxorubicin-induced cardiac toxicity in rats. J. Egypt. Nat. Can. Inst., 17(4): 291-300.

Attia SM, Bakheet SA, Al-Rasheed NM. 2010. Proanthocyanidins produce significant attenuation of Doxorubicin-induced mutagenicity via suppression of oxidative stress. Oxidat. Med. Cell. Longev., 3(6): 404-413.

Chularojmontri L, Gerdprasert O, Wattanapitayalul SK. 2013. *Pummelo* protects Doxorubicin-induced cardiac cell death by reducing oxidative stress, modifying Glutathione Transferase expression, and preventing cellular senescence. Evid.-Bas. Complem. Altern. Med., ID254835: 9 pages.

Cigremis Y, Parlakpinar H, Polat A, Colak C, Ozturk F, Sahna E, Ermis N, Acet A. 2005. Beneficial role of Aminoguanidine on acute cardiomyopathy related to Doxorubicin-treatment. Molec. Cell. Biochem., 285(1-2): 149-154.

Das RN, Poudel N. 2006. Could *Garlic* be an useful adjuvant therapy in Adriamycin failure? Kathmandu Univ. Med. J., 4(3): 337-339.

Dayton A, Salvendiran K, Maduru S, Khan M, Kuppusamy ML, Naidu S, Kalai T, Hideg K, Kuppusamy P. 2011. Amelioration of Doxorubicin-induced cardiotoxicity by an anticancer-antioxidant dual-function compound, HO-3067. Pharmacol. Exp. Ther., 339(2): 350-357.

Denev PN, Krachanov CG, Ciz M, Lojek A, Krachanova M. 2012. Bioactivity and antioxidant activity of *Black Chockeberry* (*Aronia melanocarpa*) polyphenols *in vitro* and *in vivo*: evidences and possible mechanisms of action: a review. Comp. Rev.Food Sci. & Food Safety, 11(5): 471–489.

Domarew CA, Holt RR, Goldmann-Snikoff G. 2002. A study of Russian phytomedicine and commonly used herbal remedies. J. Herb. Pharmacother., 2: 31-48.

Dudka J, Gieroba R, Korga A, Burdan F, Matysiak W, Jodlowska-Jedrich B, Mandziuk S, Korobowicz E, Murias M. 2012. Different effects of Resveratrol on dose-related Doxorubicin-induced heart and liver toxicity. Evid.-Bas. Complem. Altern. Med., ID 6061183: 10 pages.

El Benna J, Han J, Park JW, Schmid E, Ulevitch RJ, Babior BM. 1986. Activation of p38 in stimulated human neutrophils: phosphorylation of the oxidase component p47phox by p38 and ERK but not by JNK. Arch. Biochem. Biophys., 334(2): 395-400.

Granados-Principal S, Quiles JL, Ramires-Tortosa CL, Sanchez-Rovira P, Ramirez-Tortosa MC. 2010. New advances in molecular mechanisms and the prevention of Adriamycin toxicity by antioxidant nutrients. Food Chem. Toxicol., 48(6): 1425-1438.

Hafidh RR, Abas F, Abdulamir AS, Jahanshiri F, Bakar FA, Sekawi Z. 2009. A review: cancer research of natural products in Asia. Int. J. Can. Res., 5(2): 69-82.

Han X, Gao S, Cheng Y, Sun Y, Liu W, Tang L, Ren D. 2012. Protective effect of Naringenin-7-*O*-glucoside against oxidative stress induced by Doxorubicin on H9c2 cardiomyocytes. BioSci. Trends, 6(1): 19-25.

Han X, Pan J, Ren D, Cheng Y, Fan P, Lou H. 2008. Naringenin-7-*O*-glucoside protects against Doxorubicin-induced toxicity in H9c2 cardiomyocytes by induction of endogenous antioxidant enzymes. Food Chem. Toxicol., 46(9): 3140-3146.

Hovmaln Persson HA, Jeppsson N, Bartish IV, Nybon H. 2004. RAPD analysis of diploid and tetraploid populations of *Aronia* points to different reproductive strategies within the genus. Hereditas, 141(3): 301-312.

Huang S, Terstappen WMM. 1994. Lymphoid and myeloid differentiation of single human CD34+, HLA-DR+, CD38- hematopoietic stem cells. Blood, 84(6): 1515-1526.

Injac R, Strukelj B. 2008. Recent advances in protection against Doxorubicin-induced toxicity. Technol. Can. Res. Treat., 7(6): 497-516.

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Jahngen-Hodge J, Obin MS, Gong X, Shang S, Nowel TR, Gong J, Abasi H, Blumberg J, Taylor A. 1997. Regulation of ubiquitin-conjugating enzymes by Glutathione following oxidative stress. J. Biol. Chem., 272(45): 28218-28226.

Kähkönen MP, Hopia AI, Vuorela HJ, Rauha J, Piklaja K, Kajala TS, Heinonen M. 1999. Antioxidant activity of plant extracts containing phenolic compounds. J. Agric. Food Chem., 47(10): 3954-3962.

Katamura M, Iwai-Kanai E, Nakaoka M, Okawa Y, Ariyoshi M, Mita Y, Nakamura A, Ikeda K, Ogata T, Ueyama T, Matoba S. 2014. Curcumin attenuates Doxorubicin-induced cardiotoxicity by inducing autophagy via the regulation of JNK phosphorylation. Clin. Exp. Cardiol., 5.

Kokotkiewicz A, Jaremicz Z, Luczkiewicz M. 2010. *Aronia* plants: a review of traditional use, biological activities, and perspectives for modern medicine. J. Med. Food, 13(2): 255-269.

Kong J, Chia L, Goh N, Chia T, Bruillard R. 2003. Analysis and biological activities of anthocyanins. Phytochemistry, 64(5): 923-933.

Kujawska M, Ignatowicz E, Ewertowska M, Oszmianski J, Jodynis-Liebert J. 2011. Protective effect of *Chokeberry* of chemical-induced stress in rat. Hum. Exp. Toxicol., 30(3): 199-208.

Kulling SE, Rawel HM. 2008. *Chokeberry* (*Aronia melanocarpa*) – a review on the characteristic componenets and potential health effects. Planta Med., 74(13): 1625-1634.

Kwiechen I, Michalska M, Wlodek L. 2006. The selective effect of Cystathyonine on Doxorubicin hepatotoxicity in tumor-bearing mice. Eur. J. Pharmacol., 550(1-3): 39-46.

Liu X, Chen Z, Chang C, Ma Y-S, Youngberg GA, Hamdy R, Chua BHL. 2002. Melatonin as an effective protector against Doxorubicin0induced cardiotoxicity. Am. J. Physiol. Heart Circ. Physiol., 283(1): H254-H263.

Lou H, Yuan H, Ma B, Ren D, Ji M, Oka S. 2004. Polyphenols from peanut skins and their free radical-scavenging effects. Phytochemistry, 65(16): 2391-2399.

Manach C, Williamson G, Morand C, Scalbert A, Remesy C. 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am. J. Clin. Nutr., 81(Suppl.): 230S-240S.

McDonnald PP, Bald A, Cassatella MA. 1997. Activation of NF-kappaB pathway by inflammatory stimuli in human neutrophils. Blood, 89(9): 3421-3433.

Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. 2004. Pharmacol. Rev., 56(2): 185-229.

Mohamed AA, Khalil S, Nossier NS, Khalil MS. 2010. The protective role of alpha-Lipoic acid against Doxorubicin-induced cardiotoxicity in male albino rats (a light and transmission electron microscopy study). Egypt. J. Histol., 32(1): 227-234.

Oliveira PJ, Bjork JA, Santos MS, Leino RL, Froberg MK, Moreno AJ, Wallace KB. 2004. Carvediol-mediated antioxidant protection against Doxorubicin-induced cardiac mitochondrial toxicity. Toxicol. Appl. Pharmacol., 200(2): 159-168.

Ortega AL, Mena S, Estrela JM. 2011. Glutathione and cancer cell death. Cancers, 3(1): 1285-1310.

Öz E, Erbas D, Surucu HS, Duzgun E. 2006. Prevention of Doxorubicin-induced cardiotoxicity by Melatonin. Molec. Cell. Biochem., 282(1-2): 31-37.

Park E-s, Kim S-d, Lee M-h, Lee H-s, Sung J-k, Yoon Y-s. 2003. Protective effects of N-acetylcysteine and Selenium against Doxorubicin toxicity in rats. J. Vet. Sci., 4(2): 129-136.

Pavlova V, Sainova I, Alexieva B, Valkova I, Markova Tz, Nikolova E. 2014. Antioxidant effects of *Aronia melanocarpa* extract after Doxorubicin treatment. Bulg. J. Agricult. Sci., 20(Suppl.1): 188-192.

Principal SG, Quiles JL, Ramirez-Tortosa CL, Sanches-Rovira P, Ramirez-Tortosa MC. 2010. New advances in molecular mechanisms and the prevention of Adriamycin toxicity by antioxidant nutrients. Food Chem. Toxicol., 48(6): 1425–1438.

Quiles JL, Huertas JR, Battino M, Mataix J, Ramirez-Tortosa MC. 2002. Olive oil and mitochondrial oxidative stress: studies on Adriamycin toxicity, physical exercise and ageing. Toxicol., 180(1): 79-95.

Rugina D, Sconta Z, Pintea A, Bunea A, Socaciu C. 2011. Protective effects of *Chokeberry* anthocyanin-rich fraction at nanomolar concentrations against oxidative stress induced by high doses of glucose in pancreatic β-cells. Bull. UASVM Vet. Med., 68(1): 313-319.

Sadzuka Y, Matsuura M, Sonobe T. 2009. The effect of Taurine, a novel biochemical modulator, on the antitumor activity of Doxorubicin. Biol. Pharm. Bull., 32(9): 1584-1587.

Sainova I, Pavlova V, Alexieva B, Vavrek I, Nikolova E, Valcheva-Kuzmanova S, Markova Tz, Krachanova M, Denev P. 2012. Chemoprotective, antioxidant and immunomodulatory *in vitro*-effects of *Aronia melanocarpa* total extract on laboratory-cultivated normal and malignant cells. J. BioSci. Biotechnol., Special Edition from National Youth Conference "Biological Sciences for a Better Future", 19-20 October, 2012, Plovdiv, Bulgaria: 35-43.

Sainova I, Pavlova V, Alexieva B, Valkova I, Markova Tz, Nikolova E. 2014. Antioxidant effects of *Aronia melanocarpa* extract after Doxorubicin treatment *in vitro* and *in vivo*. Adv. Biores., 5(2): 119-123.

Sainova I, Pavlova V, Alexieva B, Valkova I, Markova Tz, Nikolova E. 2015. Experimental models for investigation of antioxidant and immunomodulatory effects *in vitro* of *Aronia melanocarpa* extract. Bull. Env. Pharmacol. & Life Sci., 4(2): 79-82.

Scott JM, Khakoo A, Mackey JR, Haykowsky MJ, Douglas PS, Jones LW. 2011. Modulation of Anthracycline-induced cardiotoxicity by aerobic exercise in breast cancer: current evidence and underlying mechanisms. Circulation, 124(5): 642-650.

Shad KF, Al-Salam S, Hamza AA. 2007. Sesame oil as a protective agent against Doxorubicin induced cardion toxicity in rat. Am. J. Pharmacol. Toxicol., 2(4): 159-163.

Stoner GD, Wang LS, Casto BC. 2008. Laboratory and clinical studies of cancer chemoprevention by antioxidants in berries. Carcinogenesis, 29(9): 1665-1674.

Wang H, Yu P, Gou H, Zhang J, Zhu M, Wang Z-h, Tian J-w, Jiang Y-t, Fu F-h. 2012. Cardioprotective effects of 20(S)-Ginsenosode Rh2 against Doxorubicin-induced cardiotoxicity *in vitro* and *in vivo*. Evid.-Bas. Complem. Altern. Med., 8 pages.

Wang L, Stoner GD. 2008. Anthocyanins and their role in cancer prevention. Cancer Lett., 269(2): 281-290.

REVIEW

Zapolska-Downar D, Bryk D, Malecki M, Hajdukiewicz K, Sitkiewicz D. 2012. *Aronia melanocarpa* fruit extract exhibits anti-inflammatory activity in human aortic endothelial cells. Eur. J. Nutr., 51(5): 563-572.

Zdunczyk Z, Frejnagel S, Wroblewska M, Juskiewicz J, Oszmianski J, Estrella I. 2002. Biological activity of polyphenol extracts from different plant sources. Food Res. Int., 35(2): 183-186.

Zhang S-h, Wang W-q, Wang J-l. 2009. Protective effect of tetrahydroxystilbene glucoside on cardiotoxicity induced by Doxorubicin *in vitro* and *in vivo*. Acta Pharmacol. Sin., 30(11): 1479-1487.

Zhao X, Zhang J, Tong N, Liao X, Li Z, Luo Y, Zuo H. 2011. Effects of commercial anthocyanin-rich extracts on colonic cancer and nontumorigenic colonic cell growth. J. Int. Med. Res., 39(5): 1720-1727.

Zhu W, Jia Q, Wang Y, Zhang Y, Xia M. 2012. The anthocyanin cyanidin-3-O-β-glucose, a flavonoid, increases hepatic glutathione synthesis and protects hepatocytes against reactive oxygen species during hyperglycemia: involvement of a cAMP-PKA-dependent signaling pathway. Free Radic. Biol. Med., 52(2): 314-327.

Zielinska-Przyjemska M, Olejnik A, Dobrowolska-Zachwieja A, Grajek W. 2007. Effects of *Aronia melanocarpa* polyphenols on oxidative metabolism and apoptosis of neutrophils of obese and non-obese individuals. Acta Sci. Pol., 6(3): 75-87.