Mugla Journal of Science and Technology

IMPORTANCE OF SOME METALLOIDS IN BIOLOGICAL LIFE

Merve SEZER
Department of Biology, Mugla Sıtkı Koçman University, Turkey, mmervesezerr@gmail.com
https://orcid.org/0000-0003-0947-2912
Esra DİBEK
Department of Biology, Mugla Sıtkı Koçman University, esradibek@gmail.com
https://orcid.org/0000-0002-8110-5466
Bekir ÇÖL
Department of Biology, Mugla Sıtkı Koçman University, bekircol@gmail.com
https://orcid.org/0000-0001-8997-4116

Received: 21.07.2018, Accepted: 19.11.2018 Review Article
*Corresponding author DOI: 10.22531/muglajsci.466007

Abstract

Metalloids have vital importance for some organisms. The particular relationship between the metalloid and specific biological functions should be investigated further, though there are somewhat limited scientific studies on the subject. Among the roles of this specific class of chemical elements, silicon, for instance, plays an important role in the formation of valve structures in diatoms. Boron is an essential element for plants and known to be toxic for living cells when present above a certain threshold. Arsenic and antimony are toxic metalloid elements in numerous respects. Therefore, the cells have developed biochemical and molecular strategies to protect and escape from these metalloids. Another metalloid, germanium, is one of the rare elements and although its inorganic form is toxic, its organic form is used to treat many diseases. Studies have shown that there is a high proportion of Germanium metalloid in the structure of Ganoderma lucidum used in the treatment of some diseases. In addition, tellurium-containing proteins were found in the structure of some tellurium-resistant fungi. Thus, considering all this information collectively reflects the significance of the metalloids in biological life. The aim of this study is to present the importance and roles of some metalloids in biological life.
Keywords: Metalloid, Boron, Silicon, Arsenic, Antimony, Tellurium, Germanium

BİYOLOJİK YAŞAMDA BAZI METALLOİDLERİN ÖNEMİ

Öz

Metalloidlerin bazı organizmalar için hayati öneme sahip olduğu bilinmektedir. Metalloidlerin biyolojik fonksiyonlar ile arasındaki ilişkilerin bilinmesi önem arz etmekte olup, nispeten az olmakla birlikte bu konuda bilimsel çalışmalar vardır ve çalışmaların artması gerekmektedir. Örneğin; Silikon, diyatomlardaki valf yapılarının oluşumunda önemli bir rol oynar. Bor, bitkiler için vazgeçilmez bir elementtir. Öte yandan, belirli bir eşiğin üzerinde mevcut olduğunda canlı hücreler için toksik olduğu bilinmektedir. Bir diğer örnek, arsenik ve antimon birçok yönden toksik metalloid elementlerdir. Bu nedenle, hücreler metaloitlerden korunmak ve kaçmak için biyokimyasal ve moleküler stratejiler geliştirmektedirler. Bir diğer metalloid olan germanyum nadir bulunan elementlerden olup, inorganik formu toksik olmasına karşılık organik formu birçok hastalığın tedavisinde kullanılmaktadır. Yapılan çalışmalar, bazı hastalıkların tedavisinde kullanılan Ganoderma lucidum'un yapısında yüksek oranda Germanyum metalloidinin olduğunu göstermiştir. Ayrıca bazı telluryuma dirençli mantarların yapısında telluryum içeren proteinlere rastlanmıştır. Bu bilgiler göz önünde bulundurulduğunda, metaloidlerin biyolojik yaşamda önemli yerleri olduğu dikkat çekmektedir. Bu çalışmadaki amacımız, bazı metalloidlerin biyolojik yaşamdaki önem ve rollerini derleyerek sunmaktır.
Anahtar Kelimeler: Metalloid, Bor, Silikon, Arsenik, Antimoni, Telluryum, Germanyum

Cite

Sezer, M., Dibek, E., Çöl, B., (2018). "Comparative analysis of information technologies", Mugla Journal of Science and Technology, 4(2), 236-241.

1. Introduction

Metalloid is a term used in chemical science to classify some chemical elements. This term was first used to refer to the non-metals. Until 1940-1960, the metalloids were not defined as hybrid elements, but later on the term was adopted [1].

While the elements classified as metalloids are similar to the metals with some properties, some properties are similar to the non-metals.

Each element can be classified as nonmetal or metal based on its chemical and physical properties. Metalloids contain the elements which are not fully located in these two basic classifications and are also called semi-metals. Metalloids are physically similar to metals, but chemically similar to nonmetals.

2. Metalloids and Their Status in Cellular Biology: Two Concepts

For some organisms, metalloids have vital importance.

For example; Boron is an essential metalloid for plants [3]. Silicone has an important role in the formation of valve structures in diatoms [4]. Some metalloids are harmful to cellular life at certain doses. For example; arsenic and antimony are toxic metalloid elements in numerous respects [5]. Therefore, the cell has developed biochemical and molecular strategies to protect and escape from such metalloids.

2.1. Boron (B)

Boron is mostly found in nature as borates [6]. It is difficult to use boron in practical applications because it is very fragile in its pure form. Boron is found within wide range in the earth's crust (5-100 mg/kg) [7].

At neutral pH, it is most commonly found in the form of boric acid ($B(OH)_3$). The next most common form is borate ($B(OH)_4^-$) [8]. Boron does not exist by itself, it is present as a compound with other atoms.

One of the important properties of boron is its ability to form diester bonds between *cis*-hydroxyl containing molecules. Owing to this attribute, it can play a role as a "molecular binder" [9].

2.1.1. Boron containing biomolecules

Some quorum sensing molecules such as auto inducer 2 are known to contain boron and are functional in some bacterial species [10].

It is also involved in allowing the polysaccharides of the Rhamnogalacturonan II structure to cross-link on the cell walls of the plants. This molecular binding ability of Boron in the cross-linking of rhamnogalacturonan is an important component of plant cell walls and thus making this semi-metal "essential" for the vascular plants [11].

In these examples, Boron is found in the form of a borate ester. Boron is also found in the structure of antibiotics Boromycin [12], Tartrolon A, Tartrolon B [13], Aplasmomycin [14] and Borophycin [15]. Another molecule is the Phenyl Boronic Acid (PBA) molecule found in the bacterium species *Arthrobacter nicotinovarans* [16].

2.1.2. Boron and plants

Boron-polysaccharide complexes have been isolated from the stem cell walls of tomato leaf and radish (*Raphanus sativus*). In addition, some molecules containing boron ester bonds have been detected in plant cells [17].

While boron is an essential element for the plants, relatively higher concentrations cause toxicity.

Therefore, in order to keep the boron concentration at a relatively constant and harmless level in the cell, some proteins that control the movement of boron in and out of the cell are needed and some have been identified.

Boric acid, the uncharged form of boron, can also be transported through the cell membrane by passive diffusion [18,19] and active transport [20,21].

In addition, facilitating abilities of aquaporin and aquaglyceroporins have been shown to be involved in the uptake of boron into the cell [22].

The form boron carried actively on the cell membrane is the form $B(OH)_3$ (boric acid) [18, 19, 23].

Some of the Boron carrier proteins are called BOR1, BOR4, NIP5;1, Atr1 proteins [23, 24, 25].

2.1.3. Boron and Human

The essentiality of boron for human has not been fully proven due to the lack of convincing biochemical evidence. Therefore, the debates are ongoing and this particular subject is controversial. Currently, accepted notion is that "Boron is certainly beneficial at specific doses and is probably essential" for humans and animals.

Besides this, there is evidence that Boron is nutritionally important to humans and animals. It has been shown that boron affects mammalian life processes through the use of metabolism or a multitude of substances [26, 27].

Boron plays a role in the regulation of body minerals, including calcium and vitamin D, and protects bone structure by preventing calcium and magnesium depletion [26].

2.2. Silicon (Si)

Silica is one of the most commonly found elements in the earth's crust ranking second to oxygen. Si is present in aqueous solutions in the form of $Si(OH)_4$ (silicic acid) [28].

Silicon exhibits many properties similar to the carbon element and is the most commonly suggested element for an alternative biochemical system.

The reason for this suggestion is the ability of the atom to form 4 bonds, which makes it convenient to build many compounds with different combinations, and furthermore, as in the case of methane (CH_4), can also form silane (SiH_4) with hydrogens [29].

Silicon forms 4 connected structures similar to the carbon element in the earth's crust [30].

Along with the oxidation of silicon, each silicon atom becomes solid silicon with a chemical structure in the form of a lattice surrounded by 4 oxygen atoms [28].

The elemental form of silicon is not found in nature alone [29].

2.2.1. The biogenic element Silicon

Although the contents of silicon in living things are not very high, silicon is considered as a biogenic element [31]. However, the biological role of silicon is much more limited than that of carbon. Diatoms, Radiolaria, Siliceous sponges use biogenic silica as a structural material to form the skeleton [32].

Some bacterial species called "silicate bacteria" such as some species of Bacillus genus have been shown to release silicon from aluminosilicates [33].

Biodegradation of organosiliums, which are the synthetic materials obtained by using silicon, is carried out by some microorganisms and responsible microbial enzymes have been reported [34].

Equisetum telmateia (great horsetail), *Equisetum arvense* (common horsetail), *Phalaris canariensis* has high silicon accumulation in the lemma (head) part [35]. In addition, rice is one of the plants with high silicon accumulation [36].

Accumulation of about 10% of silicon is observed, and this accumulation is necessary to protect the plant against biotic and abiotic stress factors [37].

The beneficial effects of the silicium for the plants are generally seen in the plants that accumulate and this accumulation is usually seen in the surface of the tissues [38].

2.2.2. Diatoms and Silicon

Diatom cells are hold in a single silicate (cellulosic) cell wall containing two separate valves (or shells) [39].

Biogenic silica, which is formed in the cell walls, is synthesized intracellularly by polymerization of silicic acid monomers. It is then extracellularly extended and attached to the cell wall [40].

When the concentration of silicic acid is low, SIT proteins are less visible in the cell membrane, and when the concentration is increased, the number of SIT in the cell membrane also increases. The SIT proteins are also found in the organism, in the transport silicon vesicles and in the vesicle membranes of the calcification of the silicon [41].

Silicon can be polymerized to form polysilicic acid at high concentrations. This form is used in the defense mechanism against biotic and abiotic stresses [39, 40].

2.2.3. Silicon related proteins

Lsi transporters belong to the NIP subfamily of aquaporins (nodulin26 like intrinsic proteins) [42].

This protein is regulated by the conformation of the extracellular matrix of the silicon [43].

HvLsi1 and ZmNIP2-1, ZmNIP2-2, ZmNIP2-3 homologous proteins also contribute to the uptake of silicon [44]. Although the aquaporins are bi-directional in water transport, they have been shown to have no extracellular transport in the silicon transport [44].

SITs are the proteins that actively transport silicon into the diatoms [45].

2.2.4. Medical importance

Silicon has been shown to have a specific positive effect on the hardness of the skin, hair and nails [46, 47].

Silicone dioxide, a suspension medium, tablet and capsule diluent, is used as a thickener in the pharmaceutical fields [48].

2.3. Arsenic (As)

Arsenic is found in arsenate and arsenite anions in natural waters and is generally considered to be toxic to biological systems [49].

In the earth's crust, there are 4 oxidation forms which are most common; 0, -3, +3 and +5 valued forms.

From a structural and chemical point of view, arsenate is similar to phosphates [33].

2.3.1. Arsenic in cellular environment

When the forms of arsenic in the cell are evaluated, it is observed that arsenate (pentavalent form) is reduced to arsenite (trivalent form) [50].

If arsenic ($As(OH)_3$) is present in aqueous solutions, it is predominantly more harmful than the arsenate form, and the element has a toxic effect [51].

No basic biological functions have been described for arsenic, but arsenic has been found in the structure of complex organic molecules such as arsenopyrite and arsenobetaines in the organisms such as marine algae and invertebrates [52]. Fungi and bacteria have been shown to produce volatile methylated arsenic compounds [53].

2.3.2. Intracellular uptake and chemical modifications

Arsenite is generally taken up by the aquaglyceroporins, arsenate uptake usually takes place via phosphate transport systems [54].

When it is taken into the cell, the arsenate form is reduced to arsenite by arsenate reductase enzyme with ArSC (in pl258 plasmid in *S. aureus*), Acr2p (in *S. cerevisiae*), ArsC (in plasmid R773 in *E. coli*) [55].

The arsenate form (AsV) of arsenic, H_2AsO is similar in size to H_2PO_4 (phosphate), so the phosphate transporters may allow the entry of arsenate into the cell. The examples to the phosphate transporters include PstC ABC transporters in *E. coli* and PiT-1 and PiT-2 phosphate transporters. After As(V) enters the cell, it is converted to As(III) by ArsC (arsenate reductase) [56].

Pho84p (phosphate transporter) is also capable of allowing the arsenate to pass through. [57]. The Acr2p protein encoded by the ACR2 gene is an arsenic reductase [58]. Another alternative route for As(III) is via the Ycf1p ABC transporter [59].

2.3.3. Mechanisms of toxic effects

Thiols in cysteine residues are found in the active sites of many important enzymes, arsenic binding to these regions leads to serious toxic effects because it inactivates the enzyme [60].

Arsenic disrupts ATP production through various mechanisms. The alpha-ketoglutarate dehydrogenase enzyme is inhibited by arsenite [61].

Arsenic also inhibits lipoic acid, a cofactor for pyruvate dehydrogenase [62] so affects citric acid cycle. Both arsenate reduction and arsenide oxidation are detoxification mechanisms. An enzyme group belonging to the family of S-adenosyltransferases is known to substitute methyl groups for hydroxyl groups in arsenite and antimonite [63].

2.4. Antimony (Sb)

The most common forms are pentavalent and trivalent forms. Mechanism of action of antimony has been shown to be similar to arsenic. In aqueous solutions, the trivalent form Antimonite ($Sb(OH)_3$) is present. The trivalent form was found to be much more toxic than the pentavalent form [64].

There is not sufficient evidence to show whether or not antimony plays roles in common metabolic pathways. However, one result indicates that antimony was found in the structure of lipids in the diatom, *Thalassiosira nana*. Also, antimony seems to be biomethylated in some organisms [5].

2.4.1. Antimony transport proteins

Transport of arsenite and antimony in and out of the cells can be passive or active. In passive transport routes, the aquaglyceroporins belonging to the NIP subgroup are among the channels facilitating the transport. AQP1 can facilitate the transport of antimony and arsenite in many Leishmania species [65]. Antimony has also been shown to be transported through Acr3p and ArsB. Ycf1p found in *S. cerevisiae* is a transport protein that transports arsenite and antimony [59].

2.5. Tellurium (Te)

Tellurium is an element more common in the universe than in the earth. This element is found mostly in the mines melted together with gold and silver [66].

2.5.1. The biological activities of tellurium

Tellurium is not considered necessary for biological systems. However, in the absence of sulfur, tellurium ions were seen in the amino acid and protein structures of some of the mushrooms resistant to tellurium [33].

Aspergillus fumigatus, *Aspergillus terreus* and *Penicillium chrysogenum* are tellurium resistant mushrooms. Tellurium has been regarded as toxic to most organisms. Although some resistance genes have been identified, resistance mechanisms have not been fully understood [33].

2.5.2. Tellurium resistance mechanisms

Tellurium reduction and oxidation are used in the resistance mechanisms in the organisms. For the bioremediation of tellurite, tellurate, and elemental tellurium, volatile dimethyltellurium residue, seen in some bacteria and fungi, may give clues regarding the presence of another resistance mechanism [67].

2.6. Germanium (Ge)

Although the inorganic form of germanium is toxic, the organic form is used in the treatment of some diseases [68]. This organic form is synthesized by the Asai Germanium Research Institute in Tokyo [69].

2.6.1. Germanium and Ganoderma lucidum

Ganoderma lucidum, also known as the red reishi, is used in the treatment of some diseases. Studies have shown that *Ganoderma lucidum* mushroom contains high concentrations of organic germanium. This rare mineral provides Ganoderma with some important remedial properties [70].

Recently, *Ganoderma lucidum* has been used to treat cancer [71]. According to Dr. Kazuhiko Asai's research, Ganoderma contains between 800 and 2000 ppm of germanium [72]. One of the anti-cancer agents in *Ganoderma lucidum* is germanium. Ganoderma lucidum improves liver detoxification, thereby increasing liver function and triggering liver cell restructuring. This is an extremely important herbal supplement for those with liver cancer [73].

2.6.2. Use as a medicine

As it is discussed recently, germanium is partly helpful in cancer treatment and eliminates chronic viral infections. It prevents the rise of cholesterol. The Germanium 100-300 mg per day is and can be used as supplements, which may be useful in helping treat some diseases. Germanium is also reported to be present in some plants, fungi, onion species found in in the country sides [70].

3. Conclusion

In summary, the following characteristics of metalloids are remarkable. Boron has been found to be involved in important structures in many living systems and has the ability to form diester bridges between *cis*-hydroxyl containing molecules, which makes this atom a molecular binder. Silicon is a metalloid with a similar biological structure to carbon, and its biological role in diatoms, radiolaria and sponges is very important. Arsenic has been shown to affect certain molecules that are vital to the cell, hence causing toxicity and some organisms can withstand these toxic effects through various cellular mechanisms. Antimony has attracted attention due partly to its similar structure to arsenic. Tellurium is not thought to be necessary for biological systems, but some tellurium-resistant fungi have been found to contain tellurium-containing proteins. While the inorganic forms of germanium are toxic, their organic forms have been considered potentially useful in some disease treatments.

4. Acknowledgment

We would like to thank TUBİTAK (114Z987) and Muğla SK University BAP division (pr no 17/101).

5. References

[1] Atkins P., Overton T., Rourke J., weller M., Armstrong F., “Shriver & Atkins' inorganic chemistry”, 5th ed., Oxford University Press, Oxford, ISBN 1429218207, 2010.
[2] Krannich L.K. & Watkins C.L. 2006, 'Arsenic: Organoarsenic chemistry,' Encyclopedia of inorganic chemistry, 2012.
[3] Warrington K. The effect of boric acid and borax on the broad bean and certain other plants. Annals of Botany. ;37:629–672, 1923.
[4] Rita A. Horner (2002). A taxonomic guide to some common marine phytoplankton. Biopress. pp. 25–30. ISBN 978-0-948737-65-7, 2013.
[5] Gallicchio L., Fowler B. A., Madden E. F., “Arsenic,Antimony and Bismuth”. Patty's Toxicology 2001.
[6] Greenwood NN & Earnshaw A, “Chemistry of the elements, 2nd ed., Butterworth-Heinemann”, ISBN 0750633654, 2002.
[7] Shorrocks, V.M. The occurrence and the correction of boron deficiency. Plant Soil 193, 121–148, 1997.
[8] Zangi R. and Filella M. “Transport routes of metalloids into and out of the cell: A review of the current knowledge.” Chemico-Biological Interactions, Spain, 11s, 2012.
[9] Savant N.K., Snyder G.H., Datnoff L.E. “Silicon management and sustainable rice production”, Adv. Agron 58 151–199, 1997.
[10] Chen X, Schauder S, Potier N, Van Dorsselaer A, Pelczer I, Bassler BL, Hughson FM. “Structural identification of a bacterial quorum-sensing signal containing boron.” Nature, USA, 545-9., 2002.
[11] O'Neill MA, Eberhard S, Albersheim P, Darvill AG. “Requirement of borate cross-linking of cell wall rhamnogalacturonan II for Arabidopsis growth.” USA, 2001.
[12] Kohno J, Kawahata T, Otake T, Morimoto M, Mori H, Ueba N, Nishio M, Kinumaki A, Komatsubara S, Kawashima K. “Boromycin, an anti-HIV antibiotic.” Japan, 1996.
[13] Irschik H, Schummer D, Gerth K, Höfle G, Reichenbach H. “The tartrolons, new boron-containing antibiotics from a myxobacterium, Sorangium cellulosum”. Germanium, 1995.
[14] Okami,Y., Okazaki, H., Kitahara, T., Umezawa, H. “New antibiotic, aplasmomycin, produced by a Streptomycete isolated from shallow sea mud.” J. Antib. Studies on marine microorganisms.5.29, 1019-1025. 1976.
[15] Arai M., Koizumi Y., Sato H., Kawabe T., Suganuma M., Kobayashi H., Tomoda H., Omura S. “Boromycin abrogates bleomycininduced G2 checkpoint.” J. Antib. 57, 662–668. 2004
[16] Negrete-Raymond Ac, Weder B, Wackett LP. “Catabolism of arylboronic acids by Arthrobacter nicotinovorans strain PBA.” Appl Environ Microbiol, USA. 2003
[17] Benner, K., Klufers, P. “Polyol metal complexes part 36–a combined X-ray and NMR study of borate esters of furanoidic cis-1,2-diols.” Carbohydr. Res. 327, 287–292. 2000.
[18] Raven J.A. “Short and long-distance transport of boric acid in plants”, New Phytol. 84 231–249. 1980.
[19] Dordas C., Brown P.H. “Permeability of boric acid across lipid bilayers and factors affecting it”, J. Membr. Biol. 95–105. 2000.
[20] Dannel F., Pfeffer H., Romheld V. “Characterization of root boron pools, boron uptake and boron translocation in sunflower using the stabile isotopes 10B and 11B”, Austr. J. Plant Physiol. 27 397–405. 2000.

[21] Stangoulis J.C.R., Reid R.J., Brown P.H., Graham R.D. “Kinetic analysis of boron transport in Chara”, Planta 213; 142–146. 2001.
[22] Durbak AR, Phillips KA, Pike S, O'Neill MA, Mares J, Gallavotti A, Malcomber ST, Gassmann W, McSteen P. “Transport of boron by the tassel-less1 aquaporin is critical for vegetative and reproductive development in maize.” Plant Cell. Jul; 26(7):2978-95. doi: 10.1105/tpc.114.125898, 2014.
[23] Dordas C., Brown P.H. Evidence for channel mediated transport of boric acid in squash (Cucurbita pepo), Plant Soil 235 95–103. 2001.
[24] Takano, J. et al. “The Arabidopsis major intrinsic protein NIP5;1 is essential for efficient boron uptake and plant development under boron limitation.” Plant Cell 18, 1498–1509, 2006.
[25] Kaya A., Karakaya H. C., Fomenko D. E., Gladyshev V. N., Koc A. “Identification of a Novel System for Boron Transport: Atr1 Is a Main Boron Exporter in Yeast”. Mol Cell Biol. Jul; 29(13): 3665–3674, 2009.
[26] Nielsen F.H. “Evidence for the nutritional essentiality of boron,” J. Trace Elem. Exp. Med. 9; 215–229, 1996.
[27] Nielsen F.H., Penland J.G. “Boron supplementation of peri-menopausal women affects boron metabolism and indices associated with macromineral metabolism, hormonal status and immune function,” J. Trace Elem. Exp. Med. 12 251–261. 1999.
[28] Muller, W.E.G. “Silicon Biomineralization: Biology, Biochemistry, Molecular Biology, Biotechnology” Springer-Verlag, Berlin. 2003.
[29] Bains, W., Tacke, R. “Silicon chemistry as a novel source of chemical diversity in drug design.” Curr. Opin. Drug Discov. Dev. 6, 526–543. 2003.
[30] Chuck R. "Similarities of Silicon & Carbon." Sciencing,https://sciencing.com/similarities-silicon-carbon-8508022.html, 2017.
[31] Exley, C. "Silicon in life:A bioinorganic solution to bioorganic essentiality". Journal of Inorganic Biochemistry. 69 (3): 139–144, 1998.
[32] Emanuel E. "SILICON". Annual Review of Plant Physiology and Plant Molecular Biology. 50: 641–664. 1999.
[33] Tomas R., Sigler K. “Biologically active compounds of semi-metals.” Phytochemistry 69, 585–606, 2007.
[34] Lukasiak J., Dorosz A., Falkiewicz B., Prokopowicz M., Rosciszewski P., “Biodegradation of Silicones (Organosiloxanes)” Chapter: Biodegradation of Silicones (Organosiloxanes). In: Biopolymers, 10.1002/3527600035.bpol9024, 2002
[35] Labun P., Grulova D., Salamon I., Sersen F., “Calculating the Silicon in Horsetail (Equisetum arvense L.) during the Vegetation Season”, Food and Nutrition Sciences, 4, 510-514, 2013.
[36] Ueno N. M., Yamaji N., Ma J. F., “High Silicon Accumulation in the Shoot is Required for Down-Regulating the Expression of Si Transporter Genes in Rice”, Plant and Cell Physiology, Volume 57, Issue 12, 1 December, Pages 2510–2518, 2016.
[37] Gao, J.P., Chao, D.Y., Lin, H.X. “Understanding abiotic stres tolerance mechanisms: recent studies on stress response in rice.” J. Int. Plant Biol. 49, 742–750, 2007.
[38] Richmond, K.E., Sussman, M. “Got silicon? The non-essential beneficial plant nutrient. Curr. Opin”. Plant Biol. 6, 268–272. 2003.
[39] Jezequel V. M., Hildebrand M., Brzezinski M.A. “Silicon metabolism in diatoms:implications for growth. “J.Phycol. 36, 821-840. 2000.
[40] Racki, G.; Cordey, F. “Radiolarian palaeoecology and radiolarites: is the present the key to the past?”. Earth-Science Reviews 52: 83–120. 2000.
[41] Marron, A. O., Ratcliffe, S., Wheeler, G. L., Goldstein, R. E., King, N., Not, F., Richter, D. J. “The Evolution of Silicon Transport in Eukaryotes. Molecular Biology and Evolution, 33 (12), 3226–3248, 2016.
[42] Ma J.F., Tamai K., Yamaji N., Mitani N., Konishi S., Katsuhara M., Ishiguro M., Murata Y., Yano M. “A silicon transporter in rice,” Nature 440 688–691. 2006
[43] Chiba Y., Mitani N., Yamaji N., Ma J.F. HvLsi1 is a silicon influx transporter in barley, Plant J. 57 810–818, 2009.
[44] Bienert G.P., Thorsen M., Schussler M.D., Nilsson H.R., Wagner A., Tamas M.J., Jahn T.P. “A subgroup of plant aquaporins facilitate the bi-directional diffusion of As(OH)3 and Sb(OH)3 across membranes, “BMC Biol. 6 26. 2008.
[45] Hildebrand M., Volcani B.E., Gassmann W., Schroeder J.I. “A gene family of silicon transporters,” Nature 385 688–689. 1997.
[46] 30. Lassus A. “Colloidal silicic acid for oral and topical treatment of aged skin, fragile hair and brittle nails in females,” J. Int. Med. Res. 21 209–215. 1993
[47] Barel A., Calomme M., Timchenko A., Paepe K.D., Demeester N., Rogiers V., Clarys P. D. Berghe V., “Effect of oral intake of choline-stabilized orthosilicic acid on skin, nails and hair in women with photodamaged skin,” Arch. Dermatol. Res. 297 147–153. 2005.
[48] Van Veen B., Bolhuis G. K., Wu Y. S., Zuurman K., Frijlink H. W. “Compaction mechanism and tablet strength of unlubricated and lubricated (silicified) microcrystalline cellulose.” European Journal of Pharmaceutics and Biopharmaceutics, 59, 133–138 (2005).
[49] Shankar, S., Shanker, U., & Shikha. “Arsenic Contamination of Groundwater: A Review of Sources, Prevalence, Health Risks, and Strategies for Mitigation.” The Scientific World Journal, 2014, 304524, 2014.
[50] Hoffman R.D., Lane M.D. “Iodophenylarsine oxide and arsenical affinity chromatography: new probes for dithiol proteins,” J. Biol. Chem. 267 14005–14011. 1992.
[51] Menzel D.B., Hamadeh H.K., Lee E., Meacher D.M., Said V., Rasmussen R.E., Greene H., Roth R.N. “Arsenic binding proteins from human lymphoblastoid cells,” Toxicol. Lett. 105 89–101. 1999.
[52] Edmonds, J.S., Francesconi, K.A., Cannon, J.R., Raston, C.L., Skelton, B.W., White, A.H.,. “Isolation, crystal structure and synthesis of arsenobetaine, the

arsenical constituent of the western rock lobster Panulirus longipes cygnus" George. Tetrahedron Lett. 18, 1543-1546. 1977.

[53] Bentley R, Chasteen T.G. "Microbial methylation of metalloids: arsenic, antimony, and bismuth." Microbiol Mol Biol Rev. USA, 2002.

[54] Rosen B.P. "Biochemistry of arsenic detoxification." FEBS Lett. Oct 2;529(1):86-92 USA, 2002.

[55] Zegers I., Martins J.C., Willem R., Wyns L., Messens J. "Arsenate reductase from S. aureus plasmid pI258 is a phosphatase drafted for redox duty." Nat Struct Biol. Oct;8(10):843-7, 2001.

[56] Villa-Bellosta R., Sorribas V. "Role of rat sodium/phosphate cotransporters in the cell membrane transport of arsenate." Toxicol Appl Pharmacol., Oct 1;232(1):125-34, 2008.

[57] Maciaszczyk-Dziubinska, E., Wawrzycka, D., & Wysocki, R. "Arsenic and Antimony Transporters in Eukaryotes." International Journal of Molecular Sciences, 13(3), 3527–3548. 2012

[58] Mukhopadhyay, R., & Rosen, B. P. "Arsenate reductases in prokaryotes and eukaryotes". Environmental Health Perspectives, 110 (Suppl 5), 745–748,2002

[59] Paumi, C. M., Chuk, M., Snider, J., Stagljar, I., Michaelis, S. "ABC Transporters in Saccharomyces cerevisiae and Their Interactors: New Technology Advances the Biology of the ABCC (MRP) Subfamily. Microbiology and Molecular Biology Reviews : MMBR, 73(4), 577–593, 2009.

[60] Shen, S., Li, X.-F., Cullen, W. R., Weinfeld, M., Le, X. C. "Arsenic Binding to Proteins." Chemical Reviews, 113(10), 7769–7792, 2013.

[61] Kulshrestha A, Jarouliya U, Prasad G, Flora S, Bisen PS. "Arsenic-induced abnormalities in glucose metabolism: Biochemical basis and potential therapeutic and nutritional interventions." World J Transl Med; 3(2): 96-111, 2014.

[62] Bergquist, E. R., Fischer, R. J., Sugden, K. D., Martin, B. D. Inhibition by methylated organo-arsenicals of the respiratory 2-oxo-acid dehydrogenases. Journal of Organometallic Chemistry, 694(6), 973–980, 2009

[63] Challenger F., "Biological methylation", Chem. Rev. 36, 315–361, 1945.

[64] Gebel T. "Arsenic and antimony: comparative approach on mechanistic toxicology", Chem.-Biol. Interact. 107 131–144, 1997.

[65] Frézard, F., Monte-Neto, R., & Reis, P. G. "Antimony transport mechanisms in resistant leishmania parasites." Biophysical Reviews, 6(1), 119–132, 2014.

[66] Cook N. J., Ciobanu C. L., Spry P. G., Voudouris P. "Understanding gold-(silver)-telluride-(selenide) mineral deposits" Episodes Vol. 32, no. 4, 2009.

[67] Chasteen T. G., Bentley R. "Biomethylation of Selenium and Tellurium: Microorganisms and Plants" Chem. Rev. 103, 1, 1-26, 2003.

[68] Ishiwata Y., Yokochi S., Hashimoto H., et al. "Protection against concanavalin A-induced murine liver injury by the organic germanium compound, propagermanium." Scand.J Immunol.;48(6):605-614, 1998.

[69] Nakamura T., Nagura T., Sato K., Ohnıshı M. "Evaluation of the Effects of Dietary Organic Germanium, Ge-132, and Raffinose Supplementation on Caecal Flora in Rats." Bioscience of Microbiota, Food and Health, 31(2), 37–45, 2012.

[70] Babu P. D. and Subhasree R. S., "The Sacred Mushroom "Reishi"". American-Eurasian Journal of Botany, 1 (3): 107-110, 2008.

[71] Jin X., Beguerie R. J., D.M. Sze , Chan G.C., "Ganoderma lucidum (Reishi mushroom) for cancer treatment." Cochrane Database Syst Rev. Apr 5;4: 2016

[72] Asai K., "Miracle Cure: Organic Germanium", Japan Publications, Inc.; 1st edition 1980.

[73] Su, Z. Y., Sun Hwang, L., Chiang, B. H., Sheen, L. Y. "Antihepatoma and Liver Protective Potentials of Ganoderma Lucidum (Ling Zhi) Fermented in a Medium Containing Black Soybean (Hēi Dòu) and Astragalus Membranaceus (Shēng Huáng Qí)." Journal of Traditional and Complementary Medicine, 3(2), 110–118, 2013.