Silica particles inhibit sporozoite invasion, promote IgE, inhibit CYP3A4 and provoke bursting of infected erythrocytes

Opinion

Chronic inhalation of crystalline silica is an occupational hazard that results in silicosis due to the toxicity of silica particles to lung cells. It is thus surprising to read that silica Nanoparticles are extensively applied for drug delivery. Silica particles are used as conveyors of drugs with low bioavailability. Even for artemether. Silica Nanoparticles have the advantage of a high specific surface area and can therefore guest a considerable amount of drug. Silica may enhance in some cases the vaccination efficiency. In vitro internalization of silica particles has also been described to stimulate macrophages to release inflammation promoting mediators.

Silica and immunoglobulins E

Silica may boost the immune system and stimulate IgE production. This effect is known since 40 years. IgE is probably the most important item in acquired humoral activity against malaria. A single dose of standard quartz with particle size <5μm is able to stimulate in Balb/c mice the production of IgE and GI1 antibody.

Silica in plants and in Artemisia

This mineral has barely been studied in plants. Plants take up silicon as mono-silicic acid and later it is deposited in its polymerized form as amorphous hydrated silica. Major silica depositions occur in root endodermis, leaf epidermal cells and trichomes. The ability of a plant to accumulate Si varies greatly between species. It is up to 2% in wheat, rice, oats, close to 0 % in flowers, and intermediate in kitchen and medicinal herbs: 0.4 % in spinach, 0.1 in ginseng, 0.32%, in parsley, 0.56 in salvia, 0.56 in tilia, 0.26 % in dill, 0.67 in inula, 0.6 in hibiscus, 0.61% in mint, 0.35% in Artemisia annua, 0.22% in Artemisia absinthium, 0.57% in Artemisia frigida, but only 0.002% in Artemisia maritima. Horsetail (Equisetum arvense) and nettle (Urtica dioica) containing 1.1% silica were used in Europe against malaria.

In many plants silica is present in the form of phytoliths in cell walls for their strengthening. Families with high phytolith production are Acanthaceae, Aceraceae, Annonaceae, Asteraceae, Artemisia tridentata and Artemisia spicata for example contain phytoliths. Phytoliths are present in the glandular trichomes of the plants. Trichomes are fine outgrowths or appendages on plants. Trichomes serve as the plant’s phalanx of little shields responsible for the developing protection against fungus and insects. The presence of trichomes is ubiquitous in the genus Artemisia. 15 taxa were examined to this effect to be used as taxonomic markers. Food products have been shown to contain silica in the nanometer size range (i.e. 5–200nm). Rats orally exposed to silica nanoparticles saw a 1.5 to 2 times increase of the silica content in lung, kidney, liver, brain, testis, spleen but no clear target organ could be identified after 28 days of exposure. The trial showed accumulative properties, and the particles were retained in liver and spleen for at least 4 weeks.

Bioavailability of silica particles does not depend on particle size. The bioavailability of nanoparticles versus their bulk counterparts was evaluated in rats after a single oral administration and intravenous injection, respectively. The results demonstrated that all bulk materials had slightly higher crystallinity than nanoparticles, however, their dissolution properties were not affected by particle size. No significant difference in oral absorption and bioavailability was found between nano and bulk-sized materials. Silica nanoparticles are retained for over 30 days in the tissues because of the endocytosis by macrophages. African diet is rich in cereals and starch, loaded in silicium, even bananas, thus promoting IgE build-up. European food contains more vegetables, fruits, milk products, meat, very poor in silicium.

Silica, sporozoites and Kupffer cells

Since several decades it is suspected that Kupffer cells have a supportive role in the homing of sporozoites. Macrophages were thought to act as a barrier to sporozoite entry in liver cells. Evidence is gathering for a possible dual role of macrophages under different sets of conditions. Before activation macrophages might act as transporting agents of sporozoites to the parenchymal cells of the liver. It is now recognized that Kupffer cells function as portals for malaria sporozoites to the liver. They are the resident macrophages of the liver and should phagocyte sporozoites. These traverse Kupffer cells, yet suffer no harm. It seems plausible that Plasmodium evolution produced sporozoites with the ability to manipulate Kupffer cell function. They have learned to use Kupffer cells as an affable portal and hepatocytes as a relatively secure niche and nutritional “Schlaraffenland” (land of plenty), thereby providing a jump start towards a successful blood infection.

It was already recognized 30 years ago that silica particles might strongly affect sporozoite uptake in the liver. A reduction in Kupffer cell number and activity, induced by silica treatment, resulted in a very significant decline in uptake of infective sporozoites Plasmodium yoelii nigeriensis by the perfused liver and a parallel fall in the successful infection of the host by inoculated sporozoites in vivo. Silica treatment produced no significant detectable pathological changes in hepatocytes. Light microscopy revealed some focal degeneration in the blood vessels of silica-treated animals, but the sinusoids remained unaffected except that the numbers of Kupffer cells were markedly reduced. Scanning electron microscopy confirmed that the silica treatment had little effect on the structure of the capillaries and sinusoids. This evidence suggests that the silica pretreatment reduces the phagocytic properties of liver by specifically removing Kupffer...
cells. The uptake of sporozoites is significantly reduced in silica-treated livers with 59% of the original sporozoite load disappearing after 15 min perfusion.21

Macrophages internalize silica. Exposure of cultured macrophages to crystalline silica leads to cell death; however, the mechanism of cell–particle interaction, the fate of particles, and the cause of death are unknown. Eighty percent of macrophages die within 12 hours of silica exposure. Latex beads of the same size are also phagocytosed rapidly but do not lead to macrophage death. Macrophages gather particles by extending protrusions. These draw the particles to the cell body where they stick avidly.22 Kupffer cells stimulated by silica nanoparticles release large amounts of reactive oxygen species, tumor necrosis factor-α and nitric oxide. Silica particles also increase production of interleukin-6. This oxidative and inflammatory burst is evidently detrimental for sporozoites.23–25 Silica particles also adsorb hydrogen peroxide and other peroxides present in Artemisia and its infusion, these stabilized peroxides progressively attack Kupffer cells.26 silica treated mice were challenged with Plasmodium berghei. A dose up to 5mg per mouse before challenge resulted in protection of the animal. No mortality was recorded in mice which received silica alone (35 mg; 5 mg/day x 7 days). Death due to lethal Pberghei infection could be delayed or prevented by altering/reducing the functional activities of macrophages during the course of infection.27 Before recommending the administration of silica against malaria caution however is recommended. As described previously silica particles affect the population and functionality of macrophages. And this may have a detrimental effect on the resistance against other infections. It was shown for example that the inoculation of silica a few days before infecting mice intraperitoneally with Salmonella typhimurium severely reduced the survival of these mice.28

Interaction of silica particles with erythrocytes

Incubation of erythrocytes with silica nanoparticles caused a dose-dependent hemolytic effect. Transmission electron microscopy analysis revealed that the particles are taken up by erythrocytes. Lipid erythrocyte susceptibility to in vitro peroxidation measured by malondialdehyde showed a significant and dose-dependent increase.29–30 The influence of five varieties of silica dust on lipid peroxidation in erythrocytes was studied in vitro. All the varieties of silica dust investigated induced a significantly higher level of lipid peroxides than was found in the control samples. The hemolysis produced by silica dust was associated with the formation of an appreciable amount of malonaldehyde, indicating peroxidative cleavage of the polysaturated fatty acids. The results obtained suggest that lipid peroxidation of membrane-bound polysaturated fatty acids may be involved in the cytotoxic activity of SiO2 dust.31,32

Silica particles also have an effect on erythrocyte morphology. They become swollen and take irregular shapes and even fragment.33 The authors of this paper conclude that amorphous silica nanoparticles cause dose-dependent hemolytic effects and remarkably alter the shape and deformability of erythrocytes. The abilities of OH elimination is inhibited to facilitate ROS accumulation in erythrocytes. Silica nanoparticles induce a dose-dependent ROS production, leading to oxidative damage of erythrocyte membrane by increasing the lipid peroxidation and decreasing the antioxidant ability, consequently causing hemolysis. ATPase activities are inhibited, and the energy metabolism disorder of membrane contributes to the hemolytic effects in human erythrocytes. In vitro studies on the destruction (lysis) of red blood cells by some silicate minerals showed the reaction to be complete in less than one hour and very destructive to the cell membrane. Surprisingly, the activity of silica was stronger for silica than for chrysotile (asbestos). Aluminium oxide and hydroxydioxide did not show this hemolytic effect.34,35

The human malaria parasite Plasmodium falciparum drastically changes the volume and morphological properties of the host cell. Malaria-infected erythrocytes are characterized by a complex ultrastructure with knobs, caveolae and clefts. This is an open door for silica entrance, further increasing the osmotic pressure, and provoking bursting of the erythrocyte before the schizont-trophozoites maturation is completed. The action of silica particles on erythrocytes may be similar to the toxicity they have on bacteria. Authors of a recent study have demonstrated the bactericidal effect of these nanoparticles to both susceptible and even multiple resistant E. coli, in which the free-antibiotic could not efficiently kill the bacteria. This occurs because the nanoparticle itself can also kill the bacteria.29

Silica particles and CYP3A4

Because silica nanoparticles are used in food and drugs, their effects on metabolic enzymes such as cytochrome P450s (CYPs) are of particular interest. Xenobiotics such as drugs are metabolized by CYPs which are expressed at the highest levels in the liver. Cytochrome P450 3A4 (CYP3A4) is involved in the metabolism of approximately half of the drugs in use. Drugs, some foods and beverages affect the activity of CYPs. For example grapefruit juice inhibits CYP3A4 activity and thus can lead to side effects when taken with drugs metabolized by CYP3A4. In contrast, St. John’s wort induces CYP3A4 and thus reduces the efficacy of some drugs that undergo CYP3A4-dependent metabolism. Nanomaterials have also been reported to affect CYP3A4 activity. The small size and high surface area of nanomaterials give them useful properties such as unique chemical reactivity; therefore, silica nanoparticles have the opportunity to react with CYPs. Some recent work from Japan clearly shows that silica nanoparticles inhibit CYP3A4, again more than ketoconazol, the strongest inhibitor known.35–38 Previously Japanese authors had shown that silica nanoparticles may drastically enhance the efficacy or toxicity of chemicals.39,40

Artemisia plants are known for their strong CYP3A4 and CYP2B6 inhibition activities. In a pioneering study in 2010, the University of Louvain had studied the anti-inflammatory effect and modulation of cytochrome P450 activities by Artemisia annua tea infusions in human intestinal Caco-2 cells.41 These assays were done on aqueous infusions of Artemisia annua samples from 7 different origins. For all samples there was a significant reduction in the CYP3A4 activity with the highest reduction down to 37% of the control value for the sample from Luxembourg (registration number MNHNL17732 at the herbarium of Luxembourg). Ketoconazol, a well-known specific and potent CYP3A4 inhibitor used for comparison at 50μM, completely inhibited the CYP3A4 activity. Artemisinin, rosmarinic and chlorogenic acids tested at plausible intestinal concentrations had no effect on the CYP3A4 activity. More recently similar assays were run at the Vrije Universiteit Brussel. They used ethanolic extracts 32 gr dried leaves of Artemisia plant material extracted by Soxhlet in 9 hours. They worked with Artemisia plants from different origins, including the species Artemisia abrotanum, Artemisia apiacea, Artemisia pontica, Artemisia herba alba, Artemisia absintium, Artemisia afra.

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The CYP3A4 inhibition was surprisingly high for all Artemisia samples, up to 6 times higher than the for ketoconazol (0.11µg/mL) or for diluted grapefruit juice. This is surprising because grapefruit juice has the reputation to be the strongest CYP3A4 inhibitor from plant origin. Surprising is also the fact that all Artemisia samples show CYP3A4 inhibition, except one.43 This is confirmed by a recent study from Egypt on the extracts of 57 medicinal plants. Generally aqueous extracts have a stronger effect than ethanolic extracts. Among all these plants, for a concentration of 100µg/ml, Artemisia annua and Artemisia capillaris are ranking at the top with a few others with an inhibition of 83.96 and 82.36%, respectively. No difference thus between the two species, indicating that artemisinin plays no role.45

Conclusion

It has been demonstrated elsewhere that high IgE levels strongly decrease the gametocyte concentration.44,45 If silica particles truly have such a dramatic effect on sporozoite invasion, on drug efficacy, on infected erythrocytes and on gametocytes one may wonder why all the laboratories desperately looking for a solution to the alarming malaria catastrophe ignored this possibility. May be all studies are based on in vitro efficiencies of potential antimalarials against parasites. Silica particles have no direct toxic effect on sporozoites, merozoites, trophozoites, gametocytes, at least no scientific paper describes a similar effect. These particles like other nano clay particles don’t have a toxic effect on Paramaecium caudatum either.46 May be because most of the studies are based on extracts obtained with organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances. May be Bigpharma is looking desperately for new organic molecules for new antimalarial monotherapies and silica particles are based on organic solvents, and this approach ignores minerals and hydrophilic substances.

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Conflict of interest

None.

References

1. Jaywant NP, Harita RD, Kailas KM, et al. Exploring the potential of porous silicas as a carrier system for dissolution rate enhancement of artemether. Asian Journal of Pharmaceutical Sciences. 2016;11(6):760–770.
2. Pierre Lutgen. Antibodies, prophylaxis, transmission. Pharm Pharmacol Int J. 2018;6(1):54–57.
3. Aminian O, Sharifian SA, Mehrdad R, et al. Humoral immune system alterations in silica exposed workers. Iranian J Publ Health. 2008;37(3):142–145.
4. Masse D, Voisine C, Henry F, et al. Increased vaccination efficiency with apoptotic cells by silica-induced, dendritic-like cells. Int Arch Allergy Immunol. 1983;71(3):279–281.
5. Mancino D, Buono G, Minucci M, et al. Adjuvant effects of crystalline silica on IgE and IgG1 antibody production in mice. Int Arch Allergy Immunol. 1983,71(3):279–281.
6. Giuseppe T, Antonio T, Piro A. Folk medicine used to heal malaria in Calabria (southern Italy). J Ethnobot Ethnomed. 2010;6:27.
7. Hodson MJ, White PJ, Mead A, et al. Phylogenetic variation in the silicon composition of plants. Ann Bot. 2005;96(6):1027–1046.
8. Mancino D, Buono G, Minucci M, Adjuvant effects of crystalline silica on IgE and IgG1 antibody production in mice. Int Arch Allergy Immunol. 1983,71(3):279–281.
9. Heath AC, Carole CP. Silica in Plants: Biological, Biochemical and Chemical Studies. Ann Bot. 2007;100(7):1383–1389.
10. Smis A, Aincin MFJ, Struyf E, et al. Determination of plant silicon content with near IR reflectance spectroscopy. Front Plant Sci. 2014;5:496.
11. Rahimi R, Rabani M. Mineral contents of some plants used in Iran. Pharmacognosy Res. 2010;2(4):267–270.
12. Mikhail Blimnikov. Phytotherapies in plants and soils of the interior Pacific Northwest, USA. Review of Paleobotany and Palynology. 2005;135(1-2):71–98.
13. Cristina R, Caroline MM, Taisa CO, et al. Si-Accumulation in Artemisia annua Glandular Trichomes Increases Artemisinin Concentration, but Does Not Interfere In the Impairment of Toxoplasma gondii Growth. Front Plant Sci. 2016;7:1430.
14. Hayat MQ, Ashraf M, Khan MA, et al. Diversity of foliar trichomes and their systematic implications in the genus Artemisia. International Journal of Agriculture and Biology. 2009;11(5):542–546.
15. Van Der Zande M, Vandebriel RJ, Groot MJ, et al. Sub-chronic toxicity study in rats orally exposed to nanostructured silica. Part Fibre Toxicol. 2014;11:8.
16. Kim MK, Lee JA, Jo MR, et al. Bioavailability of Silica, Titanium Dioxide, and Zinc Oxide Nanoparticles in Rats. J Nanosci Nanotechnol. 2016;16(6):6580–6586.
17. Vreden SG. The role of Kupffer cells in the clearance of malaria sporozoites from the circulation. Parasitol Today. 1994;10(8):304–308.
18. Klots C, Frevert U. Plasmodium yoelii sporozoites modulate cytokine profile and induce apoptosis in murine Kupffer cells. Int J Parasitol. 2008;38(14):1639–1650.
19. Sinde R, Smith JE. The role of the Kupffer cell in the infection of rodents by sporozoites of Plasmodium: uptake of sporozoites by perfused liver and the establishment of infection in vivo. Acta Trop. 1982;39(1):11–27.
20. Renee MG, Gaurav NJ, Knecht DA. The Phagocytosis of Crystalline Silica Particles by Macrophages. Am J Respir Cell Mol Biol. 2008;39(5):619–627.
21. Chen Q, Xue Y, Sun J. Kupffer cell-mediated hepatic injury induced by silica nanoparticles in vitro and in vivo. Int J Nanomedicine. 2013;8:1129–1140.
22. Allison C, Harington JS, Birbeck M. An examination of the cytotoxic effects of silica on macrophages. J Exp Med. 1966;124(2):141–154.
23. Rocha-Parise M, Santos LM, Danoiseaux JG, et al. Lymphocyte activation in silica-exposed workers. Int J Hyg Environ Health. 2014;217(4-5):586–591.
24. Lewandowski D, Bajerlein D, Grzegorz S. Adsorption of hydrogen peroxide on functionalized mesoporous silica surfaces. Structural Chemistry. 2014;25(3):1505–1512.
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27. Pillai CR, Devi CU, Choudhury DS, et al. Role of macrophages in experimental malaria: IV—Bioassay of silica in immunity against Plasmodium berghei infection. *Indian J Exp Biol*. 1997;35(8):861–865.

28. O’Brien AD, Scher I, Formal SB. Effect of silica on the innate resistance of inbred mice to Salmonella typhimurium infection. * Infect Immun.* 1979;25(2):513–520.

29. Nemmar A, Beegam S, Yuvanraj P, et al. Interaction of amorphous silica nanoparticles with erythrocytes in vitro: role of oxidative stress. *Cell Physiol Biochem*. 2014;34(2):255–265.

30. Kettiger HE. Silica nanoparticles and their interaction with cells: a multidisciplinary approach. PhD Thesis: Basel; 2014. 175p.

31. Silvia Gabor, Zoe Anca. Effect of silica on lipid peroxidation in the red cells. *Internationales Archiv für Arbeitsmedizin*. 1974;32(4):327–332.

32. Slawson V, Adamson AW, Mead JF. Autodestruction of polyunsaturated fatty esters on silica. *Lipids*. 1973;8(3):129–134.

33. Jiang L, Yu Y, Li Y, et al. Oxidative damage and energy metabolism disorder contribute to the hemolytic effect of amorphous silica nanoparticles. *Nanoscale Res Lett*. 2016;11(1):57.

34. Oscarson DW, Van Scyoc GE, Ahlrichs JL. Lysis of erythrocytes by silicate minerals. *Clays and Clay Minerals*. 1986;34(1):74–80.

35. Waldecker M, Dasanna AK, Lanzer M, et al. Differential time-dependent volumetric and surface area changes and delayed induction of new permeation pathways in P falciparum infected erythrocytes. *Cell Microbiol*. 2012;14(2):e12650.

36. Capeletti LB, De Oliveira LF, Gonçalves Kde A, et al. Tailored Silica–Antibiotic Nanoparticles: Overcoming Bacterial Resistance with Low Cytotoxicity. *Langmuir*. 2014;30(25):7456–7464.

37. Shanjii I, Yasuo Y, Yuki M. Size and surface modification of amorphous silica particles determine their effects on the activity of human CYP3A4 in vitro. *Nanoscale Res Lett*. 2014;9(1):651.

38. Beatrice C, Sonia F, Barbara O, et al. Immobilization of CYP3A4 Enzyme onto SBA-15-like Mesoporous Silica and Porous Silicon Matrices.

39. Nishimori H, Kondoh M, Isoda K, et al. Influence of 70 nm silica particles in mice with cisplatin or paraquat-induced toxicity. *Pharmazie*. 2009;64(6):395–397.

40. Li X, Kondoh M, Watari A, et al. Effect of 70-nm silica particles on the toxicity of acetaminophen, tetracycline, trazodone, and 5-aminosalicylic acid in mice. *Pharmazie*. 2011;66(4):282–286.

41. Melillo de Magalhães P, Dupont I, Hendrickx A, et al. Anti-inflammatory effect and modulation of cytochrome P450 activities by Artemisia annua tea infusions in human intestinal Caco-2 cell. *Food Chem*. 2012;134(2):864–871.

42. Lazaridi Kristina. Influence of the chemical composition of Artemisia annua on CYP3A4 activity and antioxidant ability. VUB Master Thesis; 2014.

43. Ashour ML, Youssef F, Gad HA, et al. Inhibition of CYP3A4 activity by extracts from 57 plants used in TCM. *Pharmacogn Mag*. 2017;13(50):300–308.

44. Pierre Lutgen. Antibodies, prophylaxis, transmission. *Pharm Pharmacol Int J*. 2018;6(1):54–57.

45. Lawaly R, Konate L, Paul R, et al. Impact of mosquito bites on gametocyte prevalence in asymptomatic chronic Plasmodium falciparum infections and correlations with IgE and IgG titers. *Infect Immun*. 2012;80(6):2240–2246.

46. Kryuchkova M, Danilushkina A, Lvov Y, et al. Evaluation of toxicity of nanoclays in vivo: a Paramecium caudatum study. *Environ Sci Nano*. 2016;3:442–452.