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Review Article

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Azithromycin, Vitamin E, and Selenium: Their Uses in Health and Disease

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Abstract

Azithromycin is a macrolide antibiotic subclass azalides. It is generated from erythromycin and has a 15-membered lactone ring thanks to the addition of a nitrogen atom that has been swapped with methyl. By interfering with their ability to synthesize proteins, it stops bacteria from expanding. It prevents the translation of mRNA by attaching to the bacterial ribosome's 50S subunit. Certain bacterial infections, most frequently those that result in middle ear infections, strep throat, pneumonia, typhoid, bronchitis, and sinusitis, are treated or prevented using azithromycin. Its main purpose in recent years has been to protect babies and those with weakened immune systems from bacterial infections. Additionally, it works well against some STDs, including chlamydia, cervicitis, and nongonococcal urethritis. Nearly a century has passed since the discovery of vitamin E (-tocopherol). The body prefers -tocopherol above the other eight vitamin E-related compounds found in the basic diet, despite the fact that all of them are peroxyl radical scavengers. The regulatory mechanisms that assist to retain -tocopherol and excrete the non-tocopherol forms are crucial to vitamin E's biological activity. Ataxia is a neurologic abnormality that is present in severe vitamin E insufficiency, and it can lead to death. Selenium is critically important to maintaining health. It is a crucial part of various important metabolic processes, such as the metabolism of thyroid hormones, antioxidant defense mechanisms, and immunological function. Therefore, there are a number of potential public health ramifications of the drop in blood selenium content in several parts of the world, particularly in light of the high frequency of chronic diseases including cancer and cardiovascular disease. On the basis of blood glutathione peroxidase activity, recommended dietary intakes of selenium were first suggested ten years ago. Since then, 30 novel selenoproteins have been discovered, 15 of which have been purified such that their biological role can be characterized. This review gives an overview on the use of azithromycin, vitamin E, and selenium in health and disease.

KEYWORDS
Azithromycin, Vitamin E, Selenium

INTRODUCTION

Azithromycin (AZM) is a macrolide antibiotic that is effective against a wide variety of bacterial and mycobacterial infections. It has been given to patients infected with the coronaviruses SARS-CoV or MERS-CoV because it has additional anti-viral and anti-inflammatory capabilities. It is now being researched as a potential candidate treatment for SARS-CoV-2 after being discovered as a candidate therapeutic for this virus by both *in vitro* and in silico drug screens. AZM inhibits the *in vitro* replication of various viruses, including rhinovirus, influenza A, Zika virus, Ebola, enteroviruses, and coronaviruses, through a variety of methods. AZM promotes the production of anti-viral pattern recognition receptors as well as the generation of anti-viral type I and III interferon responses. AZM exhibits anti-inflammatory effects, including inhibition of IL-1beta, IL-2, TNF, and GM-CSF, which is relevant to severe coronavirus-19 illness (COVID-19), which is marked by an over-exuberant innate inflammatory response. By reducing calcineurin signaling, mammalian target of rapamycin activity, and NFB activation, AZM suppresses T cells. AZM specifically targets granulocytes, where it concentrates in lysosomes, influencing neutrophil accumulation, adhesion, degranulation, and death (Oliver and Hinks, 2021).

In the 1920s, vitamin E, an important nutrient, was identified. Numerous physiological benefits of vitamin E, such as its antioxidative properties, have been carefully studied. Reactive oxygen species (ROS), which can be produced both endogenously and exogenously, alter the redox balance in a way that contributes to a number of disorders and is also thought to be necessary for survival. Due to its high concentration among the lipid soluble vitamin groups and widespread presence throughout the entire body, vitamin E is known to control redox balance in the body (Darwish *et al*., 2020).

Selenium is integrated into selenoproteins, which have a variety of pleiotropic effects, from the synthesis of active thyroid hormone to antioxidant and anti-inflammatory actions. The importance of selenoproteins to health has come to light over the past ten years as a result of the finding of disease-associated polymorphisms in selenoprotein genes. Low selenium levels have been linked to a higher mortality risk, weakened immune system, and cognitive impairment. Selenium has antiviral properties, is necessary for both male and female reproduction to be effective,

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and lowers the risk of autoimmune thyroid disease. Selenium deficiency can lead to various viral infections. Higher selenium status has typically been associated with a reduced risk of prostate, lung, colorectal, and bladder cancer, but study results have been inconsistent, which likely accentuates the fact that supplementation will confer benefit only if intake of a nutrient is inadequate. Adding more selenium to persons who currently consume a healthy amount of the mineral could raise their chance of developing type 2 diabetes. The unbreakable U-shaped relationship between status and selenium's health effects must be emphasised; while higher intakes of selenium may be beneficial for those with low status, those with adequate to high status may suffer negative effects and shouldn't take selenium supplements (Rayman, 2012).

The objectives of this review were to throw the light on AZM, vitamin E, and selenium and their uses in health and disease.

Pharmacokinetics in lung infections

Azithromycin accumulates in epithelial cells, fibroblasts, lymphocytes, and alveolar macrophages, where concentrations can be 400 to 1,000-fold higher than in serum. Chemotactic drug delivery enhances local drug concentrations by releasing stored azithromycin by blood phagocytes and other cells that migrate into sick and inflamed tissues (Beigel *et al*., 2020). This medication has high lung tissue penetration and long-term drug concentrations (Tyteca *et al*., 2002). Azithromycin can be administered 500 mg orally every day for 3-5 days, or 500 mg on day 1 followed by 250 mg orally every day on days 2-5 (Zheng *et al*., 2014). The appropriate dosage in viral infections, however, is unknown. Several regimens are indicated in community-acquired pneumonia (CAP) IDSA guidelines, depending on severity: for outpatients, 500 mg 1 day and 250 mg thereafter for 3-5 days, whereas for severe patients, 500 mg OD for 5 days (Lucchi *et al*., 2008). 500 mg OD for 10 days is being evaluated in the recovery study, which is assessing the possible role of azithromycin in COVID-19 (Metlay *et al*., 2019).

Azithromycin is reported to destroy human malaria asexual blood stage parasites by inhibiting protein synthesis, similar to how it works against pneumonia. However, *in vitro* studies of azithromycin's antimalarial properties have revealed a capacity to inhibit pathogenic invasion, and research into the lysosomotropic properties of several macrolides has revealed a collective proclivity to impede subsequent viral replication via endolysosomal processing. CD147 is a cell-surface erythrocyte receptor implicated in inflammatory leukocyte migration and the activation of matrix metalloproteinases (MMPs) (Muramatsu, 2016). It was discovered in 2011 that it is required for *P. falciparum* merozoite invasion by directly interacting with PfRh5, a parasite ligand required for blood-stage growth (Crosnier *et al*., 2011).

Mechanism of action of azithromycin

Azithromycin, like other macrolide antimicrobials, binds to the 23S region of the 50S bacterial ribosomal subunit and suppresses protein synthesis by blocking aminoacyl-tRNA and the developing protein from transiting through the ribosome. When compared to erythromycin, azithromycin is less likely to dissociate from the Gram-negative ribosome, giving it a higher efficacy against Gram-negative infections. Azithromycin, like other macrolides and protein-synthesis inhibitors, is largely a bacteriostatic drug, which means it suppresses bacterial growth rather than immediately destroying organisms. However, azithromycin has been proven to have a bactericidal effect against some bacteria such as streptococci and H. influenza, especially at higher doses (Jelić and Antolovi, 2016). Azithromycin travels fast from the bloodstream into tissues and, once there, easily penetrates cellular membranes, allowing efficacy against intracellular pathogens (Goldman *et al*., 1990).

Azithromycin inhibits the 50S ribosome found in the parasite apicoplast, an endosymbiosis-derived organelle with bacteria-like protein-synthesis machinery that performs critical metabolic functions in non-bacterial organisms (Biddau and Sheiner, 2019). Azithromycin is a strong immunomodulator that has been demonstrated to significantly reduce airway neutrophilia, IL-8 gene expression, and C-reactive protein levels in lung transplant recipients (Verleden *et al*., 2006).

Adverse effects of azithromycin

Azithromycin is widely thought to be a safe antibacterial drug, with few patients discontinuing treatment due to side effects (Ioannidis *et al*., 2001). It is also thought to be safer and to have less cardiac side effects than other macrolides (such as erythromycin and clarithromycin). Like other macrolides, azithromycin can cause QTc prolongation and has been linked to torsades de pointes and polymorphic ventricular tachycardia. In a large retrospective cohort analysis, azithromycin use was associated with a slight but statistically significant absolute increase in cardiovascular death, as well as an increased risk of cardiovascular death when compared to amoxicillin. These findings were especially striking in participants with the highest baseline cardiovascular risk (Ray *et al*., 2012). However, among a sample of young and middle-aged people, another large cohort research failed to identify an increased risk of mortality from cardiovascular causes (Svanström *et al*., 2013). Azithromycin is also rarely associated with hepatotoxicity, which primarily manifests as hepatocellular injury within 1 to 3 weeks of treatment. Cholestatic jaundice and increased transaminase concentrations are clinical markers of hepatotoxicity (Martinez *et al*., 2015).

As with other macrolides, gastrointestinal side effects such nausea and diarrhoea are prevalent. All macrolides activate intestinal motilin receptors, which enhance stomach motility in a dose-dependent manner. (Clinicians often prescribe erythromycin for the treatment of gastroparesis due to this mechanism.). Azithromycin hypersensitivity events, such as anaphylaxis and Stevens-Johnson syndrome (SJS), are exceedingly rare (Nappe *et al*., 2015).

Contraindications of azithromycin

Azithromycin is not recommended for patients who have a history of severe hypersensitivity to azithromycin or another macrolide antibiotic (e.g., anaphylaxis or SJS). Clinicians should use caution when taking azithromycin with other drugs that lengthen the QTc interval (e.g., antipsychotics). Patients receiving the first-generation antipsychotic pimozide should avoid taking azithromycin. Macrolide antimicrobials suppress CYP3A4, the same cytochrome that metabolises pimozide; concurrent use of azithromycin and pimozide can result in hazardous plasma concentrations of pimozide, potentially leading to fatal arrhythmias. While azithromycin is a low inhibitor of CYP3A4 in comparison to other macrolides, it is nevertheless best to avoid this interaction (Westphal, 2000). Patients who have a history of cholestatic jaundice or hepatic dysfunction linked to the use of azithromycin are not advised to take it, as are those who have a history of hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibacterial agent, any ingredient in the formulation,

or any part of the container (Mylan Pharmaceuticals ULC, 2018).

Vitamin E

Tocopherols and tocotrienols, two categories of the family of fat-soluble vitamins that contain vitamin E, are classified into four isomers (alpha, beta, gamma, and delta). Although studies have shown that vitamin E also has anti-inflammatory properties, it is well known for being a potent antioxidant. In particular, neuroprotection, cardiovascular health, skin health, and bone health are all benefited by vitamin E's essential qualities (Mohd Zaffarin *et al*., 2020).

Sources of vitamin E

According to Herrera and Barbas (2001), vegetable oils (olive, soya bean, palm, maize and whole grains) are the main dietary sources of vitamin E in the human body. Evans and Bishop discovered vitamin E in 1922, and it was first synthesized in 1938. It is the term used to refer to both tocotrienols and tocopherols collectively. Alpha-tocopherol is the most active and favoured by the human body among alpha-, beta-, gamma-, delta-, tocopherol and tocotrienol forms. These compounds are all scavengers of peroxyl radicals. Because it is abundantly present in foods like wheat germ, soybeans, seeds, and vegetable oils, vitamin E deficiency in healthy individuals is uncommon. It can happen more commonly in older persons, smokers, and those who have certain gastrointestinal disorders. This indicates that the disorder of absorption is most frequently to blame for the shortage. The antioxidant and anti-inflammatory effects of vitamin E are what attract medical attention (Nazrun *et al*., 2011).

Functions of vitamin E

An important fat-soluble antioxidant called vitamin E stops the oxidation of polyunsaturated fatty acids (PUFAs) and scavenges peroxyl radicals. The generation of peroxyl radicals is halted and further oxidation of PUFAs in the membrane is avoided when vitamin E is present because peroxyl radicals interact with -tocopherol rather than lipid hydroperoxide. Tocopherol dimers are formed when glutathione or vitamin C decrease tocopheroxyl radicals, which are created from -tocopherol and peroxyl radicals and can then be further oxidised or act as prooxidants. Given that the redox state controls the activity of signalling enzymes, vitamin E's antioxidant activity may be to blame for the regulation of a number of enzymes involved in signal transmission. Protein phosphatase 2A is activated by vitamin E, enhancing PKC- dephosphorylation and reducing protein kinase C (PKC) activity. Vitamin E has been reported to inhibit PKC in a variety of cells, which has been linked to reduced platelet aggregation, decreased monocyte, macrophage, and neutrophil proliferation, reduced proliferation of vascular smooth muscle cells, and decreased superoxide production in neutrophils and macrophages (Traber, 2007).

The lipid mediator-producing enzymes or the transport proteins involved in signal transduction may both directly bind to vitamin E. The activity of signal transduction enzymes may change as a result of vitamin E's potential impact on the interaction of membrane proteins and the translocation of enzymes to the plasma membrane (Zingg, 2015).

Adverse effects of vitamin E

The risk of hemorrhagic stroke, nausea, headaches, and changes in vision, gastrointestinal discomfort, mildly elevated urine creatinine, and necrotizing enterocolitis are typical adverse effects of alpha-tocopherol intake. Due to vitamin E's ability to prevent platelet aggregation, there is a chance of increased intraoperative bleeding. It hasn't been demonstrated in those who aren't already taking antiplatelet or anticoagulants, though. If a patient is taking drugs that inhibit or induce these enzymes, monitoring for drug interactions is advised (Zingg, 2015). Alpha-tocopherol is metabolized in the liver by CYP450 enzymes.

Selenium

Selenium is a trace mineral that only occurs in very small amounts in the body but has a significant impact on human health. Brazil nuts, seeds, mushrooms, fish, shellfish, meat, and poultry are among the foods high in selenium (Shreenath *et al*., 2022).

Both the organic and inorganic forms of selenium have better than 90% bioavailability; the organic form is found in plant food as selenomethionine, and the inorganic forms are found in supplements as selenate and selenite. The duodenum of the small intestine is where selenium absorption takes place mostly. The form of selenium affects the absorption mechanism. Selenite is absorbed through simple diffusion, whereas selenate would require the use of an active sodium pump to exchange selenate with OH via cotransport sodium selenate. (Vendeland *et al*., 1994).

In the human body, selenium performs a number of roles. In order to catalyze the creation of thyroid hormone, it participates in enzymatic processes (Wojciechowska-Durczynska and Lewinski, 2017). Selenium is essential for immune system function since studies show that it helps the body fight off infections, particularly those that are viral in nature (Rayman, 2000). Selenoproteins, which include selenium, operate as an antioxidant to guard against reactive oxygen and nitrogen species (Tinggi, 2008).

Mechanism of action of selenium

Selenium exhibits a variety of action mechanisms. Selenium is incorporated into numerous proteins to form selenoproteins, which are a major factor in many of the varied actions of selenium. Through cellular metabolism, selenium reduces oxidative damage by acting as a cofactor for glutathione peroxidase (Tinggi, 2008). Selenium and vitamin E together shield cell membranes and organelles from oxidative damage. As a result, selenium can strengthen the immune system and the host's defense mechanisms. The production of active thyroid hormone by selenium is what establishes its importance in the endocrine system. Iodothyronine deiodinase, an enzyme that converts inactive thyroid hormone (T4) into active thyroid hormone (T3), interacts with the mineral (Shreenath *et al*., 2022).

Adverse effects of selenium

Supplementing with selenium has extremely little side effects. The majority of the negative effects are caused by selenium sulphide. The more frequent negative effects include skin irritation that leads to contact dermatitis, such as redness, burning, itching, and stinging; scalp sores; increased oiliness; hyperpigmented nails; and increased oiliness (Sánchez and Torres, 1984).

CONCLUSION

This review highlighted the importance of AZM in the control of many of the bacterial diseases, its pharmacokinetics, and con-

traindications. Moreover, the uses of vitamin E, and selenium in health and disease were discussed.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Beigel, J.H., Tomashek, K.M., Dodd, L.E., 2020. Remdesivir for the treatment of Covid-19-preliminary report. Reply. New England J. Med. 383, 994-994.

Biddau, M., Sheiner, L., 2019. Targeting the apicoplast in malaria. Biochem. Soc. Trans. 47, 973-983.

Crosnier, C., Bustamante, L.Y., Bartholdson, S.J., Bei, A.K., Theron, M., Uchikawa, M., Mboup, S., Ndir, O., Kwiatkowski, D.P., Duraisingh, M.T., Rayner, J.C., 2011. Basigin is a receptor essential for erythrocyte invasion by Plasmodium falciparum. Nature 480, 534-537.

Darwish, W.S., Chen, Z., Li, Y., Wu, Y., Chiba, H., Hui, S.P., 2020. Identification of cadmium-produced lipid hydroperoxides, transcriptomic changes in antioxidant enzymes, xenobiotic transporters, and pro-inflammatory markers in human breast cancer cells (MCF7) and protection with fat-soluble vitamins. Environ. Sci. Pollu. Res. 27, 1978-1990.

Goldman, R.C., Fesik, S.W., Doran, C.C., 1990. Role of protonated and neutral forms of macrolides in binding to ribosomes from gram-positive and gram-negative bacteria. Antimicrob. Agents Chemother. 34, 426-431.

Herrera, E., Barbas, C., 2001. Vitamin E: action, metabolism and perspectives. J. Physiol. Biochem. 57, 43-56.

Ioannidis, J.P., Contopoulos-Ioannidis, D.G., Chew, P., Lau, J., 2001. Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. J. Antimicrob. Chemother. 48, 677-689.

Jelić, D., Antolović, R., 2016. From erythromycin to azithromycin and new potential ribosome-binding antimicrobials. Antibiotics 5, 29.

Lucchi, M., Damle, B., Fang, A., De Caprariis, P.J., Mussi, A., Sanchez, S.P., Pasqualetti, G., Del Tacca, M., 2008. Pharmacokinetics of azithromycin in serum, bronchial washings, alveolar macrophages and lung tissue following a single oral dose of extended or immediate release formulations of azithromycin. J. Antimicrob. Chemother. 61, 884-891.

Martinez, M.A., Vuppalanchi, R., Fontana, R.J., Stolz, A., Kleiner, D.E., Hayashi, P.H., Chalasani, N., 2015. Clinical and histologic features of azithromycin-induced liver injury. Clin. Gastroenterol. Hepatol. 13, 369-376.

Metlay, J.P., Waterer, G.W., Long, A.C., 2019. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. Am. J. Respir. Crit. Care Med. 200, E45–E67.

Mohd Zaffarin, A.S., Ng, S.F., Ng, M.H., Hassan, H., Alias, E., 2020. Pharmacology and pharmacokinetics of vitamin E: Nanoformulations to enhance bioavailability. Inter. J. Nanomed. 15, 9961-9974

Muramatsu, T.B., 2016. CD147, a multifunctional transmembrane glycoprotein with various binding partners, J. Biochem. 159, 481e490.

Mylan Pharmaceuticals ULC, 2018. PrMylan-Azithromycin. Product monograph. Mylan Pharmaceuticals ULC. https://pdf.hres.ca/dpd_pm/00043815.PDF

Nappe, T.M., Goren-Garcia, S.L., Jacoby, J.L., 2015. Stevens-Johnson syndrome after treatment with azithromycin: an uncommon culprit. Amer. J. Emerg. Med. 34, 676-e1.

Nazrun, A.S., Norazlina, M., Norliza, M., Nirwana, S., 2011. The anti-inflammatory role of vitamin E in prevention of osteoporosis. Adv. Pharmacol. Sci. 2012, 142702.

Oliver, M.E., Hinks, T.S., 2021. Azithromycin in viral infections. Rev. Med. Virol. 31, e2163.

Ray, W.A., Murray, K.T., Hall, K., Arbogast, P.G., Stein, C.M., 2012. Azithromycin and the risk of cardiovascular death. New England J. Med. 366, 1881-1890.

Rayman, M.P., 2000. The importance of selenium to human health. The lancet 356, 233-241.

Rayman, M.P., 2012. Selenium and human health. The Lancet 379, 1256-1268.

Sánchez, J.L., Torres, V.M., 1984. Double-blind efficacy study of selenium sulfide in tinea versicolor. J. Amer. Acad. Dermatol. 11, 235-238.

Shreenath, A.P., Ameer, M.A., Dooley, J., 2022. Selenium deficiency. StatPearls Publishing, PMID: 29489289.

Svanström, H., Pasternak, B., Hviid, A., 2013. Use of azithromycin and death from cardiovascular causes. New England J. Med. 368, 1704-1712.

Tinggi, U., 2008. Selenium: its role as antioxidant in human health. Environ. Health Peven. Med. 13, 102-108.

Traber, M.G., 2007. Vitamin E regulatory mechanisms. Annu. Rev. Nutr. 27, 347-362.

Tyteca, D., Van Der Smissen, P., Mettlen, M., Van Bambeke, F., Tulkens, P.M., Mingeot-Leclercq, M.P., Courtoy, P.J., 2002. Azithromycin, a lysosomotropic antibiotic, has distinct effects on fluid-phase and receptor-mediated endocytosis, but does not impair phagocytosis in J774 macrophages. Exper. Cell Res. 281, 86-100.

Vendeland, S.C., Deagen, J.T., Butler, J.A., Whanger, P.D., 1994. Uptake of selenite, selenomethionine and selenate by brush border membrane vesicles isolated from rat small intestine. Biometals 7, 305-312.

Verleden, G.M., Vanaudenaerde, B.M., Dupont, L.J., Van Raemdonck, D.E., 2006. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Amer. J. Resp. Critical Care Med. 174, 566-570.

Westphal, J.F., 2000. Macrolide–induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. British J. Clin. Pharmacol. 50, 285.

Wojciechowska-Durczynska, K., Lewinski, A., 2017. Search for relevant indications for selenium supplementation in thyroid diseases. Neuroendocrinol. Letters 38, 4.

Zheng, S., Matzneller, P., Zeitlinger M., 2014. Development of a population pharmacokinetic model characterizing the tissue distribution of azithromycin in healthy subjects. Antimicrob. Agents Chemother. 58, 6675–6684.

Zingg, J.M., 2015. Vitamin E: a role in signal transduction. Ann. Rev. Nutr. 35, 135-173.