I & Vision
Research Centre

Post-terrestrial Vision, Pomegranate Dreams (ft. Tardigrade Genes)
Part II

(L to R): Mikhail Nilov; © The Trustees of the British Museum, In Spagnoli (2019); Hotpot AI; Clement Percheron. Centre: ~850 BC Neo-Assyrian seal, Pomegranate Tree of Life. Coincidental similarity to spaghetti eggs of *Macrobiotus shonaicus*

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Part II: Pomegranate Dreams & Tardigrade Genes

Gene Editing for Space Migration

Moss Piglet Morphin' Times

On to the tardigrade, since no article about space or survival is complete without them.

Commonly dubbed 'water bear' or 'moss piglet', there are over 1400 species with a plethora of habitable zones for this microinvertebrate, ranging from the vacuum of space, to – 270 C°, to an unusually exhibitionist species found in the moss of Tsuruoka's urban parking lots. Indeed, in a set of simulations by Sloan *et al.* (2017) for global sterilisation events, based on a set of general characteristics, the extremophiles hypothetically persisted until the end of days for our host star or obliteration of the third rock from it by a 250 mile wide asteroid. Before anyone gets too excited about invincibility, a biologist responding to the paper noted that in reality, and in his lab, they are 'quite easily murdered' by the thousands. Their genetic acitivity in cosmic contexts is being investigated using NASA's Bioculture System aboard the space station.

Tardigrade talents, perhaps built upon their intrinsically disordered proteins (IDPs) like Damage Suppressor (Dsup), may have applications to protect astronauts and others against ionising radiation, reactive oxygen species, cancer, the effects of microgravity, and confer overall extreme resilience (Kasianchuk *et al.*, 2023). As a therapeutic, it is believed that Dsup could be used to reduce oxidative stress, performing even better against single strand breaks in combination with the antioxidant N-acetyl-L-cysteine (NAC) (Ibid.). As a pretty substantial downside, Dsup seems to promote toxicity, DNA damage, and chromatin rearrangement in human neurons (Escarcega *et al.*, 2023).

Found in plants and some micro-organisms, late embryogenesis-abundant proteins (LEA) promote intracellular membrane tolerance in the face of abiotic stressors and are another kind of tardigrade disordered protein. They are fundamental for the stress tolerance and survival of characteristically immobile plants during harsh environmental conditions, specifically cellular water deficits including drought, salinity and freezing, and osmotic change, the latter of which occurs to some degree in microgravity. Without the presence of LEAs, many plant and tardigrade communities would no longer exist, with the proteins enabling a a dry hibernation state known as anyhydrobiosis that protects lipid membranes, enzymes, and DNA during conditions of biologically lethal water loss. LEAs are currently not a major target of biomedical research. However, their effect on mitochondrial function and liposomes may hold promise for drug delivery, agriculture, water scarcity, and other aspects of imbued extremotolerance.

So, unless humans are first adaptively mutated or annihilated by cosmic radiation, perhaps some protein innovations of the tardigrade will be used to break molecular and anatomical glass ceilings for *homo sapiens*, genetically paving the way to interplanetary migration. A fitting thematic agglomeration, as genetic enhancement, synthetic gene drives (Kolbert, 2021), chimeras, and space migration (Cirkovic, 2022) remain highly fraught and bitterly controversial topics related to the future of our kind.

However… the tardigrades face an unlikely contender as humanity's route to other realms and immortality in the form of the deific pomegranate. After all, no Achaemenid Immortal guard had gold and silver water bears on their spears (Spagnoli, *et al.*, 2021).

***Punica Granatum L.*: Afterlife, Restoration, Cosmic Scenes**

If not gene hacking, protein hacking, or super-dosing spaceflight-tardigrade protein powder (can't wait to see the packaging art for that), what about popping polyphenol pills?

This summer, Afghanistan exported its first shipment of pomegranate soft drinks to the United States. Though a far cry from the economic transition of drug-to-cash-crop envisioned decades ago, it is a start, and there is growing interest in the fruit as a multi-purpose biomedical crop. According to Damien Stone's *Pomegranate: A Global History* (2017), pomegranate and opium poppy are similarly crowned, associated with fertility, and easily confused in Mediterranean art prior to 900 B.C.E. (p. 37). The two were again confused in 2017, when USAID posted a picture of an opium farmer instead of what they believed was a Kandahar Food Zone success story.

Both opium and pomegranate have been widely used and revered in historic medical practice, alluded to in Herodotus and covered in the Papyrus Ebers (Stone, 2017), though pomegranates are rather less illegal and dangerous. For Afghanistan, a rise in medical applications of fruit farming could facilitate a market revival to (eventually) replace banned opium poppy crops, as well as improve commercial viability for cultivation of the Kandahar variety, considered the best in the world. Beyond beauty or biomedical products and nutraceutical pills,

pomegranate can even be made into molasses and wine. On account of its anti-inflammatory and divine properties (and flavour), it used to be a dietary privilege of ancient Egypt's wealthiest classes (Spagnoli *et al.*, 2021).

Historically, the pomegranate was additionally revered as a fertility, kingly, and chthonic symbol in empires ranging from ancient Persia to Egypt and Assyria, eventually becoming a representation of Christian sacrifice and restoration in Catholic Spain. In myths of Egypt and Asia, pomegranate juice was used to trick rampaging, bloodthirsty goddesses like Sekhmet and Hariti, saving mankind by virtue of deceptive resemblance to human blood (Stone, 2017: 33, 97). It goes further: In Turkish myth, fifty singing pomegranates bring a beheaded bridegroom back to life:

If 'the pomegranates will love you; you need fear nothing, for they will protect you in any distress.'

'Of all trees, this is the most salutiferous to mankind'

(Kunos, then Bartram, cited in Stone, 2017: 24, 83)

Perhaps true, and the holy fruit accords not just spiritual but cellular restoration. We have advanced from using them to cross realms into the Afterlife. Instead, astronauts and cosmo-critters of the Soviet space programmes were given pomegranate as a health tonic (Ibid., p. 90-91). Currently, pomegranates are being investigated for their role in ocular immune response and cellular pathways for inflammation. Rich in antioxidants and with pharmacotherapeutic potential for neural anti-ageing, this may be better than using potentially neurotoxic tardigrade proteins.

The rind and peel are particularly rich in ellagitannins. These in combination with zinc have potent antimicrobial properties able to combat viral, bacterial, and fungal infections like herpes simplex (HSV), *Candida albicans,* and methicillin-resistant *Staphylococcus aureus* (MRSA) (Celiksoy *et al.*, 2022) Besides antimicrobial use, there are beneficial effects on several of the cellular pathways involved in oxidative stress and inflammatory cascade – therefore pain reduction as well. While results are fairly consistent, specific mechanisms still need to be illuminated.

In an *in vitro* study by Penalver-Mellado *et al.* (2023), an extract of pomegranate (Pomanox, PMX) was investigated for anti-inflammatory potential in human corneal epithelium. A major finding was significant inhibition of interleukin-8 (IL-8) after endotoxin exposure, even compared to corticosteroid dexamethasone. Cell viability in the PMX group was also highest after exposure to lipopolysaccharides (LPS) from *E. coli*. The authors caution that study size was small, but results were promising, and contribute to building up the literature for future clinical use.

Prior, pomegranate juice was found to have potential for combatting oxidative stress in the retinas of diabetic rats, increasing levels of antioxidant enzyme glutathione peroxidise (GSH-Px) and reducing oxidative end-products in diabetes mellitus groups (Tugcu *et al.*, 2017). The effect is described as 'protective', with lower DNA oxidative damage and lipid peroxidation demonstrated in immunohistochemistry of retinal tissues.

Notably, each pomegranate species, taste, environmental and nutritional profile is different. In times past, they were even 'punicologically engineered' by Soviet botanist Gregory M. Levin for survival in frostier environments (Stone, 2017: 89), although this did not include preparation for spaceflight and interplanetary cultivars. Most plants don't have a very good time off-world, by the way, which is quite relatable for our bones, immune function, and neuro-ocular tissue. Given the genetic, oxidative, and mechanical stress mechanisms involved in SANS (Ong *et al.*, 2023), the

USSR was probably on to something when cosmonaut diets specifically featured pomegranate. The anti-microbial properties of rinds and peels may have further applications in space-crop and crew disease management.

This is not to imply that exocarpic polyphenols will be able to comprehensively protect our brains plus act to compromise the cytoplasmic membranes of all fungi, facehuggers, and assorted alien pathogens. However, at least for the foreseeable medical future, an abundance of wild type and genetically diverse pomegranate species may be a good idea. Perhaps one may yield human invulnerability, as done for Esfandiyar in the *Shahnameh*. That, holy water, or dragon's blood, though the latter is less easily procured for contemporary experimentation. Anyway, the Esfandiyar formulation specifically excludes comprehensive ocular protection (spolier), and is not to be used in combination with tamarisk. These trees have similar compounds and medicinal applications to pomegranate unless applied in the format of an arrow to the face.

Hamlet, Act 2 Scene 2

To me it is a prison . . .

O God, I would be bounded in a nutshell,

and count myself a king of infinite space,

were it not that I have bad dreams. . .

Which dreams indeed are ambition, for the very

substance of the ambitious is merely the shadow of a dream.

Partially cited in in Cirkovic (2022)

Conclusion: Dreams caused by the Flight of a Rocket around a Planet and to a Moon

The pomegranate has been a prominent symbolic device in religious art, depicted by imperial craftsmen (Spagnoli *et al.*, 2021) as well as famous painters like Botticelli and Salvador Dali. In fact, Dali's painting*, Dream Caused by the Flight of a Bee Around a Pomegranate a Second Before Awakening* (1944), parallels revolutionary moments of the late 1960s: Our first journeys into space and the sight of our planet from the cosmos: Earthrise (NASA, 1968).

The successful launch of Sputnik in 1957 and the Apollo missions of 1968 and '69 transformed human attitudes and perspectives about ourselves, our planet, and the infinite beyond (Chaikin, 2007). Not only did the 'Sputnik moment' galvanise investment in research and technologies, but Apollo-related media depicting our tiny, blue oasis floating in the gaping maw of space yielded 'an unprecedented awareness of the singularity and finitude of our terrestrial home, which in turn helped catalyse the modern environmental movement across the Western world' (Alberro, 2022).

Fifty years later, part of the strategy seems to be preserving/abandoning the blue ship by rocketing off to other (uglier) ones, like Mars, Mercury, the moon, space stations, or even the radiation-soaked moons of Saturn and Jupiter. Both technological and physiological barriers are being tinkered with, some may be broken, and there's really no telling how any of this will eventually be regulated or disrupted by human events or genotoxic effects (See Grinstein, 2023).

Rather than perceiving everything pessimistically as a 6th Mass Extinction, we can think of it as being on the edge of some kind of post-terrestrial CRISPR-Cambrian explosion, complete with spaceship-weaving silkworm–tardigrade hybrids drifting about in high earth orbit farms (you never know). Furthermore, with the wealth of genotypic and molecular innovation already existent in our minds, myths, flora, and fauna, maybe Brad-Pitt-Achilles is right:

"Do you know what's there, waiting beyond that beach? Immortality. Take it! It's yours!"

(*Troy, 2004*)

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Select References – Part I & II

Alberro, H. (2022). H.G Wells, earthly and post-terrestrial futures. *Futures, 140*, pp. 102954. https://www.sciencedirect.com/science/article/pii/S0016328722000544

Cannan, W. J. and Pedersen, D. S. (2016). Mechanisms and Consequences of Double-strand DNA Break Formation in Chromatin. *J Cell Physiol, 231*(1), pp. 3–14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994891/

Celiksoy, V., Moses, R.L., Sloan, A.J. *et al.* (2022). Synergistic activity of pomegranate rind extract and Zn (II) against *Candida albicans* under planktonic and biofilm conditions, and a mechanistic insight based upon intracellular ROS induction. *Sci Rep* **12**, 19560. https://doi.org/10.1038/s41598-022-21995-7

Chaikin, A. (2007). Live from the Moon: The Societal Impact of Apollo. In S. J. Dick and R. D. Launius (Eds.) *Societal impact of spaceflight*. (Washington DC: NASA). https://history.nasa.gov/sp4801-chapter4.pdf ; Full book here: https://history.nasa.gov/sp4801.pdf

Choi, E. *et al.* (2023). Genome editing in the treatment of ocular diseases. *Experimental & Molecular Medicine*. doi: 10.1038/s12276-023-01057-2. https://www.nature.com/articles/s12276-023-01057-2

Ćirković, M.M. (2022). The nutshell kings: Why is human space settlement controversial in the first place? *Futures*. https://doi.org/10.1016/j.futures.2022.103023

(2023, September 21). CRISPR Silkworms Make Spider Silk That Defies Scientific Constraints. *Genetic Engineering & Biotechnology News.* https://www.genengnews.com/topics/genome-editing/crispr-silkworms-make-spider-silk-that-defies-scientific-constraints/

Dardona, Z. (2023). Literature Review: Punica granatum (pomegranate) with an emphasis on its anti-parasitic activity. *GSC Biological and Pharmaceutical Sciences, 23*(02), 100–114. https://doi.org/10.30574/gscbps.2023.23.2.0192

Escarcega, R. D., *et al.* (2023). The Tardigrade damage suppressor protein Dsup promotes DNA damage in neurons. *Molecular and Cellular Neuroscience, 125*, 103826. https://www.sciencedirect.com/science/article/abs/pii/S1044743123000209

Geronimo, A. (2023, August 7). The final frontier: Exploring the promise of space tourism. *Edge*. https://www.edgemiddleeast.com/space/the-final-frontier-exploring-the-promise-of-space-tourism

Grinstein, J. D. (2023, September 12). Genotoxic Effects by Base and Prime Editors in Human HSPCs Aren't Surprising, Says Pioneer. *Genetic Engineering & Biotechnology News*. https://www.genengnews.com/topics/genome-editing/genotoxic-effects-by-base-and-prime-editors-in-human-hspcs-arent-surprising-says-pioneer/

Hutton, D. (2023, March 20). Study: New gene-editing technique reverses vision loss in mice. *Ophthalmology Times*. https://www.ophthalmologytimes.com/view/study-new-gene-editing-technique-reverses-vision-loss-in-mice

Kasianchuk, N., Rzymski, P. and Kaczmarek, L. (2023). The biomedical potential of tardigrade proteins: A review. *Biomedicine & Pharmacotherapy, 158*, 114063. https://www.sciencedirect.com/science/article/pii/S0753332222014524

Kolbert, E. (2021, January 11). CRISPR and the Splice to Survive. *The New Yorker*. https://www.newyorker.com/magazine/2021/01/18/crispr-and-the-splice-to-survive

Kumar, S. *et al.* (2023). RNA-targeting strategies as a platform for ocular gene therapy. *Progress in Retinal and Eye Research, 92*, 101110. https://doi.org/10.1016/j.preteyeres.2022.101110

Kwon, D. (2023, June 20). How scientists are hacking the genetic code to give proteins new powers. *Nature Technology Feature, 618*. https://www.nature.com/articles/d41586-023-01980-4

Labant, M. (2023, June 9). Base Editors and Prime Editors Begin to Realize Their Clinical Promise. *Genetic Engineering & Biotechnology News*. https://www.genengnews.com/topics/genome-editing/base-editors-and-prime-editors-begin-to-realize-their-clinical-promise/

Maphetu, N. *et al.* (2022). Medicinal uses, pharmacological activities, phytochemistry, and the molecular mechanisms of Punica granatum L. (pomegranate) plant extracts: A review. *Biomedicine & Pharmacotherapy, 153*, 113256. https://www.sciencedirect.com/science/article/pii/S075333222200645X

Mathur, N. (2023, July 19). Understanding the mechanisms behind rising antifungal drug resistance. *News-Medical.Net*. https://www.news-medical.net/news/20230719/Understanding-the-mechanisms-behind-rising-antifungal-drug-resistance.aspx

Mi, J., Zhou, Y. Ma, S. *et al.* (2023). High-strength and ultra-tough whole spider silk fibers spun from transgenic silkworms. *Matter*. https://doi.org/10.1016/j.matt.2023.08.013

Ong, J., Tarver, W., Brunstetter, T., *et al.* (2023). Spaceflight associated neuro-ocular syndrome: proposed pathogenesis, terrestrial analogues, and emerging countermeasures. *British Journal of Ophthalmology, 107*, pp. 895-900. https://bjo.bmj.com/content/107/7/895

Paharia, P. T. (2023, August 3). Can genome editing transform ocular disease treatment?. *News-Medical.Net*. https://www.news-medical.net/news/20230803/Can-genome-editing-transform-ocular-disease-treatment.aspx

Peñalver-Mellado, M., Silva-Fuentes, F., Villar, A., Mula, A., & Zangara, A. (2023). In Vitro Anti-Inflammatory Potential of Pomegranate Extract (Pomanox®) in a Reconstituted Human Corneal Epithelium Model. *Journal of Clinical & Translational Ophthalmology*, *1*(2), 52–60. MDPI AG. Retrieved from http://dx.doi.org/10.3390/jcto1020007

Regalado, A. (2023, March 7). Forget designer babies. Here's how CRISPR is really changing lives. *MIT Technology Review*. https://www.technologyreview.com/2023/03/07/1069475/forget-designer-babies-heres-how-crispr-is-really-changing-lives/

Roberts, D.R., Albrecht, M. H., Collins, H.R., *et al*. (2017). Effects of spaceflight on astronaut brain structure as indicated on MRI. *N Engl J Med, 377*, pp. 1746–53. https://www.nejm.org/doi/full/10.1056/nejmoa1705129

Shabbir, M.A.B., Shabbir, M.Z., Wu, Q. *et al.* (2019). CRISPR-cas system: biological function in microbes and its use to treat antimicrobial resistant pathogens. *Ann Clin Microbiol Antimicrob* **18**, 21. https://doi.org/10.1186/s12941-019-0317-x

Shinojima, A., Kakeya, I., Tada, S. (2018). Association of Space Flight With Problems of the Brain and Eyes. *JAMA Ophthalmol, 136*(9), pp. 1075–1076. doi:10.1001/jamaophthalmol.2018.2635

Sloan, D., Batista, R. A. and Loeb, A. (2017). The Resilience of Life to Astrophysical Events. *Scientific Reports, 7*, 5419. https://www.nature.com/articles/s41598-017-05796-x

Spagnoli, F. (2019). The Golden Pome: The Pomegranate from its Deepest Roots to Modern Culture. *Ancient Near East Today, 7*(2). https://www.asor.org/anetoday/2019/02/Golden-Pome/

Spagnoli, F. *et al.* (2021). Archaeology, History and Symbolism. In A. Sarkhosh *et al.* (Eds) *The Pomegranate: Botany, Production and Uses*. CAB International.

Spratt, H. G. and Levine, D. (2023, June 14). Special Report on Candida auris: An Emerging Drug-Resistant Fungal Threat. *Infection Control Today*. https://www.infectioncontroltoday.com/view/special-report-on-candida-auris-an-emerging-drug-resistant-fungal-threat

Stone, D. (2017). *Pomegranate: A global history*. London: Reaktion Books.

Sundaresan, Y., Yacoub, S., Kodati, B., Amankwa, C.E., Raola, A. and Zode, G. (2023), Therapeutic applications of CRISPR/Cas9 gene editing technology for the treatment of ocular diseases. FEBS J. https://doi.org/10.1111/febs.16771

Tugcu, B., Nacaroglu, S. A., Gedikbasi, A., Uhri, M., Acar, N., & Ozdemir, H. (2017). Protective effect of pomegranate juice on retinal oxidative stress in streptozotocin-induced diabetic rats. *International journal of ophthalmology*, *10*(11), 1662–1668. https://doi.org/10.18240/ijo.2017.11.05

Qin, H. *et al.* (2023). Vision rescue via unconstrained in vivo prime editing in degenerating neural retinas. *J Exp Med, 220*(5), e20220776. https://doi.org/10.1084/jem.20220776

Xu, Y., & Li, Z. (2020). CRISPR-Cas systems: Overview, innovations and applications in human disease research and gene therapy. Computational and structural biotechnology journal, 18, 2401–2415. https://doi.org/10.1016/j.csbj.2020.08.031

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