

Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Highlights

After me, the deluge The intricacies of pulmonary surfactant

Aila Akosua Kattner*

Freelance Journalist, Berlin, Germany

ARTICLE INFO

Article history:

Received 13 December 2021

Accepted 13 December 2021

Available online 20 December 2021

Keywords:

ARDS

Surfactant

Epithelial mesenchymal transition

Pancreatic cancer

Diabetic wound healing

ABSTRACT

This issue of the *Biomedical Journal* provides a comprehensive insight into the role of pulmonary surfactant and influencing its components as well as involved molecules to treat a variety of respiratory distress disorders. We also discover how epithelial mesenchymal transition (EMT) could be targeted as part of a therapeutic strategy against lung cancer. Furthermore, a method is described to eliminate chemoresistance against gemcitabine, a drug administered to treat pancreatic cancer. We gain an insight into the composition of salivary calcium particles in periodontitis, a technique to circumvent complications in hip surgery, and a potential treatment to accelerate diabetic wound healing. Moreover, we get to know an essential oil that exerts a similar effect as diazepam on the central nervous system. A trial in patients with myofascial pain syndrome demonstrates how laser assisted trigger point therapy leads to immediate relief. Finally, a case study outlines the discovery of a genetic mutation that plays a role in intellectual disability.

Spotlight on reviews

Throughout centuries, stories of great floods have found their way into a number of mythological and religious texts. In the *Epic of Gilgamesh* for example, a Sumerian epic poem from Mesopotamia (2100 BC), it is described how the five gods decided to wipe out the humans they created by flooding the Earth.¹ Texts from later ages, that revive this topic, are the Atra-hasis (1800 BC) and the Genesis flood myth in the Hebrew Bible and the Christian Old Testament [1,2]. Similarly, the Incas have a story about a great flood that was sent to

eradicate “wicked and unruly people”.² Even in modern pop culture, movies about great deluges were immensely successful, although the origins of the catastrophes are not attributed to external forces but humanity itself: *The Day After Tomorrow* became the 6th highest grossing movie in 2004,³ 2012 was the 5th highest grossing movie worldwide in 2009.⁴

Fluid buildup in the alveoli has become an even more urgent challenge for research and healthcare since COVID-19 mortality is mainly driven by a disrupted fluid metabolism. Pulmonary edemas are a direct consequence of a severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection [3].

* Corresponding author. Freelance Journalist, Berlin, Germany.

E-mail address: aila.kattner@gmail.com.

Peer review under responsibility of Chang Gung University.

¹ <http://www.ancienttexts.org/library/mesopotamian/gilgamesh/tab11.htm>, last access 12/10/21.

² <https://www.encyclopedia.com/humanities/news-wires-white-papers-and-books/inca-mythology#:~:text=Like%20many%20peoples%2C%20the%20Incas,not%20given%20over%20to%20evil.>, last access 12/10/21.

³ https://www.boxofficemojo.com/year/world/2004/?ref=bo_cso_table_1, last access 12/10/21.

⁴ <https://www.boxofficemojo.com/year/world/2009/>, last access 12/10/21.

<https://doi.org/10.1016/j.bj.2021.12.003>

2319-4170/© 2021 Chang Gung University. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

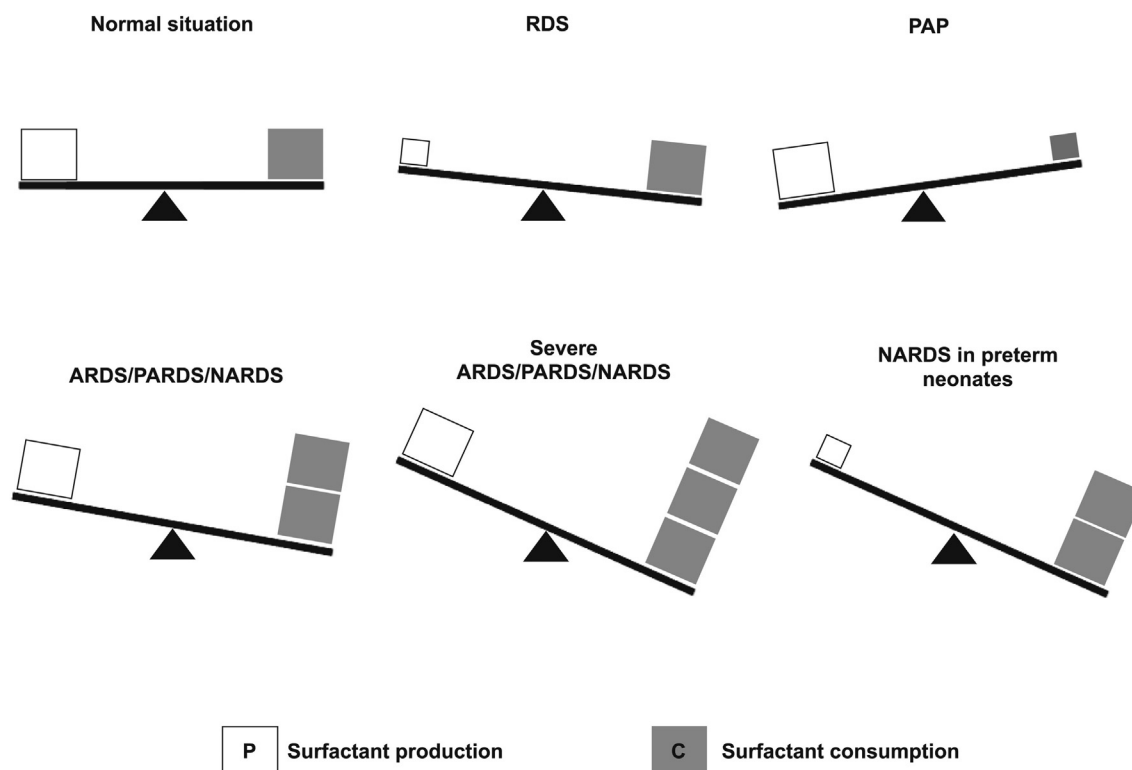


Fig. 1 The (dis-)balance between surfactant consumption and production in respiratory distress syndrome (RDS; with A = acute, P = pediatric, N = Neonatal) and pulmonary alveolar proteinosis (PAP) (Source: Luca et al. [9]).

Acute respiratory distress syndrome (ARDS) is characterized as respiratory failure due to non-cardiogenic pulmonary edema. It can be caused by an infection or sepsis through pathogens or non-pulmonary sources, severe trauma, and at times also pancreatitis or drug reactions. ARDS is divided into three categories depending on the severity of hypoxemia. The inflammation pathways activated upon the damage of lung tissue contribute on the one hand to the clearing of pathogens. However, an excessive inflammatory response might also worsen alveolar damage and further epithelial permeability, thus resulting in the accumulation of protein-rich alveolar edema fluid. Fluid accumulation in the interstitium and air space of the lungs increases the work of breathing and also causes further hypoxemia. The osmotic gradient is disrupted which additionally inhibits alveolar fluid clearance [4,5].

Pulmonary compliance is essential for the expandability of the lungs and chest wall. It is defined as the change in volume in the lungs divided by a given pressure change across the lungs. One main factor influencing lung compliance is the surface tension between the liquid/air interphase in the alveoli. The alveolar surface tension is lowered by pulmonary surfactant secreted by type II pneumocytes [6]. Pulmonary surfactant is a liquid film of specific phospholipid-proteins that covers the alveolar epithelium [7]. Surfactant is comprised of four proteins, SP-A and SP-D, which are hydrophilic. SP-B and SP-C are hydrophobic [8]. 90% of surfactant consist of lipids and about 10% are proteins [5]. The type II pneumocytes producing the surfactant are also responsible for salvaging and degrading surfactant compounds [9].

A lower surface tension increases lung compliance and prevents collapse of the lung at the end of the expiration. The lungs inflate more easily and the work of breathing is reduced [6]. Surfactant furthermore plays a role in interacting with and eliminating pathogens. Additionally, it modulates immune responses [8].

Pulmonary compliance decreases in restrictive and fibrotic lung diseases, which affect the inhalation. It is normal or increases in obstructive conditions that lead to trapped air in the lungs, thus influencing the exhalation [6].

Primary deficiencies of surfactant components can be observed in neonatal respiratory distress syndrome (NRDS) as well as a variety of acute and chronic lung disorders. In adults, secondary deficiency is possible by direct or indirect insults [7].

Increased surfactant on the other hand is a consequence of the accumulation of surfactant-derived lipoprotein compounds as in pulmonary alveolar proteinosis. The interplay although is complex: abnormal surfactant production or function is associated with lung diseases and *vice versa*, pulmonary infections alter surfactant metabolism [8].

Treatment approaches and research of ARDS include lung protective ventilation, fluid management strategies and the use of anti-inflammatory agents as well as targeting molecules and cells that stabilize endothelial and epithelial cell–cell junctions [4].

In infant RDS, therapies are used to replace and preserve surfactant [8]. In the case of neonate RDS, individualized surfactant replacement therapy needs to be initiated within three hours after birth to be most effective. However, in order

to do so, it is necessary to have reliable biological tests that are at the same time easy to use at the bedside. Autilio hence reviews currently potential candidates to evaluate surfactant status, one being the lamellar body count. The more lamellar bodies are present, the more mature the fetal lung. Qualitative tests could be performed on the stability of microbubbles in amniotic fluids or gastric aspirates as well as indirectly assessing surface tension via surfactant adsorption test [10].

Surfactant replacement therapy is not efficient in the case of secondary deficiency due to the degradation by phospholipase A2 (PLA2) enzymes [7] and has demonstrated no improvement in ARDS. Treating ARDS at an earlier stage with replacing surfactant could be promising, however, this would require recognizing the syndrome before it becomes severe [8]. Possible diagnostic markers for patients with acute lung injury are for instance isoforms of PLA2 [11].

In the editorial note of this issue, Luca and Touqui summarize the history and current progress in understanding the specificities of pulmonary surfactant. They raise awareness to the pitfalls in surfactant research over the past four decades, criticizing the lack of crosstalk between neonatal and adult intensive care, which would have promoted developing surfactant therapy approaches [12]. It seems that surfactant deficiency played a major role in infant respiratory distress syndrome (RDS) but not in acute respiratory distress syndrome (ARDS) [5]. Luca and Touqui consider surfactant therapy as promising in RDS and beyond, emphasizing that the current pandemic has sparked the interest in this topic [12].

In a further review, Luca and Autilio elucidate the current knowledge about the mechanisms of pulmonary surfactant consumption and production. The two processes are normally well balanced, ensuring low surface tension. Quantitative and qualitative disorders in this system involve surfactant catabolism and recycling [see Fig. 1]. Luca and Autilio finally evaluate strategies to protect surfactant and foster its activity, approaches include regulating secreted PLA2, whole-body hypothermia, repeated surfactant bolus or lavage with diluted surfactant solutions [9].

The mammalian PLA2 family comprises more than 30 enzymes that are sub-categorized into structurally related families [13]. The classification depends on topology, size, amino acid sequence homology, Ca^{2+} and substrate need [7]. PLA2s are released by human inflammatory cells. Several PLA2s are involved in the pathogenesis of ARDS with some showing an anti-inflammatory effect and others contributing to surfactant production [11].

Kitsiouli et al. highlight the diversity and importance of PLA2 isoenzymes expressed in ARDS. They suggest looking closer at PLA2s' spatiotemporal expression and also interactions with sets of functional cellular components for advancing the discovery of new drugs against ARDS [7].

honey bees and mole rats rely on magnetic cues to orientate themselves for the purpose of migration.⁵ In 2018, an article predicting the dangers of a geomagnetic reversal by the science journalist Alanna Mitchell shook the online community. It painted a potentially dark future for Earth's inhabitants in terms of biology, climate, cosmic radiation, and more, especially also for the modern civilization and the electronic tools it relies on.⁶ Luckily for us it seems that changes in polarity in this magnitude happen rather slowly. So slowly that humans as well as animals might adapt in time, thus escaping mass extinction.⁷

Polarity in cells is characterized by an asymmetric distribution of cell components and cytoskeleton. It plays a crucial role for specialized cell functions [14]. In epithelial tissue, polarity ensures its function as selective barrier, lining a surface of the body or an internal cavity. Furthermore, polarity plays a role in the establishment as well as maintenance of higher order epithelial tissue architecture [15]. Loss of the specific polarity is at the same time elementary for epithelial cells in order to become mesenchymal stem cells during embryogenesis or wound healing [16]. Epithelial mesenchymal transition (EMT) however also contributes to progression of diseases like organ fibrosis and cancer. Inhibiting EMT might hence be a key target for developing therapeutic strategies [17].

Niu et al. examine the effect of the microRNA mimic miR-188-5p on the EMT of lung cancer cells *in vitro*. They find that the over-expression suppresses metastasis by targeting *inter alia* the gene MGAT3 as well as the cell-adhesion molecule E-cadherin. miR-188-5p shows thus the potential of being explored both as a therapeutic candidate as well as a biomarker for the management of metastatic lung cancer [18].

“Dogs never bite me. Just humans.” [19]

When thinking about the hunter-gatherer societies of the Paleolithic age, many troublesome reasons come to mind that would endanger the survival of our ancestors back then. The nomadic lifestyle required strenuous physical activity of men, women and children, resilience to overcome harsh climate conditions, food scarcity, dangerous animals and diseases [20]. Interestingly, one of the deadliest injuries one could incur was being bitten by another human. Our understanding used to be that human-specific, infectious diseases developed during the Neolithic. However, it seems that tropical diseases have much older origins. As our hominid ancestors were still isolated in Africa, many tropical diseases rose and spread around 2.5 million to 10,000 years ago [21]. Although it has been shown that Neanderthals, who appeared around 30,000 years ago, apparently made very rudimentary use of medicinal plants to fight infections [22,23], one can assume that infections played a major role in decimating the small, nomadic tribes.

Also in this issue

Original articles

Birds flying high & fish in the sea

Earth's magnetic field plays an important role for many animal species. Among others, birds, whales, sharks, snails,

⁵ <https://www.businessinsider.com/sharks-animals-use-earth-magnetic-field-navigate-2021-5>, last access 12/7/2021.

⁶ <https://undark.org/2018/01/26/books-alanna-mitchell-spinning-magnet/>, last access 12/7/2021.

⁷ <https://www.nationalgeographic.com/science/article/earth-magnetic-field-flip-north-south-poles-science>, last access 12/7/2021.

Looking only at the bacterial inoculum that comes with a human bite wound of the current age, one finds 100 million organisms per milliliter with around 190 different species in it. Most of the pathogens that are contained in saliva flourish in the tartar of the teeth or the gingiva.⁸ Due to the number and kind of pathogens that can be present in saliva, human bite wounds are considered to be as or even more dangerous than animal bites.⁹ Being bitten by another hominoid was by the way not that uncommon in the Paleolithic age. It is hypothesized that ancestral warriors used techniques like jaw clenching to strengthen the masseter and temporalis muscles in order to inflict more lethal, defensive bites [24].

The dysbiosis of dental plaque also constitutes a pressing issue for humans of the current age, considering that it is involved in the pathogenesis of periodontitis. Peng et al. undertook the endeavor to examine in detail the composition of calcium particles in saliva that contribute to the hardening of dental plaque into calculus. The subsequent inflammation of the periodontium might finally lead to periodontitis in the presence of oral microorganisms and the pro-inflammatory compounds they produce. Peng et al. showed that the calcium-based particles in the saliva differ by size, shape and recruit different salivary proteins. They may thus contribute to different extent to the inflammation of the gingiva or on the other hand participate in antimicrobial defense [25].

Cat's whiskers in the treatment of pancreatic cancer

Pancreatic cancer is the fourth leading cause of cancer-related deaths globally [26]. The five year survival rate for it is very low with 5–10 percent. This is due to the fact that pancreatic cancer is mostly diagnosed at an advanced stage only since it shows little to no symptoms in early stages.¹⁰

The chemotherapy drug gemcitabine is part of the Model List of Essential Medicine of the WHO¹¹ and has become a standard in the treatment of pancreatic cancer since its effectiveness has been demonstrated in 1997 [27]. Unfortunately the drug has quite a number of serious side effects, since it targets fast dividing cells like cancer cells but hence also bone marrow or stomach lining.¹² Beyond that, patients may develop insensitivity to the drug due to multi-drug resistance (MDR), underlying mechanisms involve epithelialmesenchymal transition (EMT) as well as well as the h-ENT-1 protein that plays a role in the intracellular uptake of gemcitabine [26,28]. Yeyha et al. set out to investigate the effect of ethanolic extract of *Orthosiphon stamineus* on pancreatic cancer cells in comparison to rosmarinic acid plus gemcitabine [26]. The herb is also known as Java tea or Cat's

Whiskers¹³ and widely used in Asia against various ailments of kidney and bladder [29]. Yeyha et al. successfully demonstrate *in vitro* the synergistic effect of *O. stamineus* and gemcitabine, inducing cell senescence and subsequent apoptosis. Additionally, h-ENT1 expression is heightened, thus possibly reducing the expression of multidrug resistant genes [26].

When phytotherapy and 670 nm come together

Before the arrival of colonizers, there existed around 200,000 different indigenous tribes in Brazil who disposed of a vast ethnomedical knowledge [30]. *Solidago chilensis* is one of the herbs that are still used today, it has anti-inflammatory effects. In 2009, *S. chilensis* was included in the national list of native medicinal plants used by the Brazilian public health system [31].

Since wound closure in diabetics is deficient [32], the process does not follow the normal, dynamic four phases of wound healing. Wounds in diabetic patients therefore require prolonged time to heal. Moreira et al. investigated the effects of *S. chilensis* in rats either by using the herb in combination or absence of low laser therapy, which is a method to minimize burn lesions. The combination of both revealed to be superior to single application of phytotherapy or laser. The laser application allows the components of the herb to permeate the cell membrane more efficiently, eventually reducing the inflammatory phase as well as improving tissue repair by fostering angiogenesis [33].

Having a screw loose

The use of a dynamic hip screw (DHS) is primarily indicated in stable hip intertrochanteric fractures that are compressible.¹⁴ Especially in elderly patients with unstable hip fractures, excessive sliding of the lag screw and inadequate bone anchorage pose a problem [34].

Chang et al. present a retrospective cohort study on the outcomes of conventional versus bone substitute-augmented DSH (BSA-DHS) surgery in 85 patients treated for osteoporotic intertrochanteric fracture [35]. They concluded that lag screw sliding, varus collapse and femoral shortening was reduced in BSA-DHS. Also, the pain score in BSA-DHS was lower in the first six months after surgery in comparison to the conventional approach. The use of autograft or PMMA cement for augmentation has a few disadvantages. Chang et al. hence used a biphasic mixture of hydroxyapatite and beta-tricalcium phosphate¹⁵ in their study and thus successfully improved the quality of the bone-implant interface [35].

Mother's little helper¹⁶

In 2021, diazepam (originally marketed as Valium) celebrated 58 years since its market launch. For decades, benzodiazepines have caused controversy since they were over-enthusiastically prescribed at first. Only in the 1980s it became clear to clinicians then, that the class of benzodiazepines can

⁸ <https://emedicine.medscape.com/article/218901-overview>, last access 12/7/2021.

⁹ <https://www.mayoclinic.org/first-aid/first-aid-human-bites/basics/art-20056633>, last access 12/7/2021.

¹⁰ <https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/pancreatic-cancer-prognosis>, last access 12/9/21.

¹¹ <https://list.essentialmeds.org/medicines/92>, last access 12/9/21.

¹² https://www.medicines.org.uk/emc/product/2490/smpc#UNDESIRABLE_EFFECTS, last access 12/10/21.

¹³ [https://pfaf.org/user/Plant.aspx?](https://pfaf.org/user/Plant.aspx?LatinName=Orthosiphon+aristatus)

[LatinName=Orthosiphon+aristatus](https://pfaf.org/user/Plant.aspx?LatinName=Orthosiphon+aristatus), last access 12/10/21.

¹⁴ <https://www.touchsurgery.com/simulations/dynamic-hip-screw-2>, last access 12/9/21.

¹⁵ https://taiwan-pavilion.com/file/1631084284_FM.pdf, last access 12/10/21.

¹⁶ <https://www.northpointrecovery.com/drugs-in-pop-culture/>, last access 12/9/21

be largely problematic especially when used in the long run. The substance would be heavily abused and leads to dependence [36].

Traditional medicine practices around the world also include the use of essential oils (EOs). EOs are administered in various forms for their antimicrobial, antibiotic, antiviral, anti-inflammatory and antioxidant properties. Furthermore, they are beneficial against stress, and in treating depression and insomnia [37]. Kwangjai et al. present their findings on the influence of citrus EO on the central nervous system in rats. The research team concludes that the oil's effects are similar to diazepam, although in contrast to the drug, citrus EO decreases REM sleep latency and increases the total time and episode numbers of REM sleep [38].

Lighting up a traditional healing approach

Acupuncture has been used for more than 2500 years to treat chronic pain [39,40]. However, it seems that its application proves to be only partially effective in patients with chronic cervical myofascial pain syndrome (MPS). A study found that acupuncture must be received for three weeks to reduce pain in MPS significantly, the onset of symptom relief is gradual and the duration of the relief is rather short with 1.5 days [40].

Chang et al. set the objective, to compare the immediate effectiveness of low-level laser therapy (LLLT) applied on traditional acupuncture points or trigger points in cervical MPS. The group verified in a single-blinded, randomized, placebo-controlled trial the efficacy of LLLT when used on trigger points, showing that this approach immediately provides relief to patients and improves the cervical range of motion to a satisfying degree. The therapy strategy might therefore be a feasible alternative in patients with cervical MPS where classical acupuncture therapy is unavailable [39].

Brief communication

The power of words

The campaign “Spread the word to end the word” led 2010 to the passing of Rosa’s Law in the U.S. It is a federal law that commits to replacing the previously common terminology “mental retardation” in courts and diagnosis documents with “intellectual disability” (ID).^{17,18} The R-word is considered at the same time excluding as well as hurtful to people with intellectual and developmental disabilities. Still today the global engagement campaign pledges itself to not just eliminating a word, but to creating a reality where people with all intellectual and developmental disabilities are included.¹⁹

Chen and his colleagues present their findings on the whole-genome sequencing analysis of a family with two sisters diagnosed with moderate ID, schizophrenia and anxiety. The group identified a novel homozygous nonsense mutation in the *LINS1* that was transmitted to the girls from the parents who were heterozygous carriers [41].

¹⁷ <https://www.govinfo.gov/content/pkg/STATUTE-124/pdf/STATUTE-124-Pg2643.pdf>, last access 12/9/21.

¹⁸ <https://www.govinfo.gov/content/pkg/STATUTE-124/pdf/STATUTE-124-Pg2643.pdf>, last access 12/9/21.

¹⁹ <https://www.spreadtheword.global/about>, last access 12/9/21.

Conflicts of interest

The author declares no conflict of interests.

REFERENCES

- [1] Finkel IL. *The ark before Noah: decoding the story of the flood*. 1st ed. United Kingdom: Hodder & Stoughton; 2014.
- [2] Leeming DA. *Creation myths of the world: an encyclopedia*. 2nd ed. California: ABC-CLIO; 2010.
- [3] Cui X, Chen W, Zhou H, Gong Y, Zhu B, Lv X, et al. Pulmonary edema in COVID-19 patients: mechanisms and treatment potential. *Front Pharmacol* 2021;12:664349.
- [4] Huppert LA, Matthay MA, Ware LB. Pathogenesis of acute respiratory distress syndrome. *Semin Respir Crit Care Med* 2019;40:31–9.
- [5] Günther A, Ruppert C, Schmidt R, Markart P, Grimminger F, Walmrath D, et al. Surfactant alteration and replacement in acute respiratory distress syndrome. *Respir Res* 2001;2:353–64.
- [6] Edwards Z, Annamaraju P. Physiology, lung compliance. *StatPearls* 2021 Mar 27. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
- [7] Kitsioulis E, Tenopoulou M, Papadopoulos S, Lekka ME. Phospholipases A2 as biomarkers in ARDS. *Biomed J* 2021;44:663–70.
- [8] Han S, Mallampalli RK. The role of surfactant in lung disease and host defense against pulmonary infections. *Ann Am Thorac Soc* 2015;12:765–74.
- [9] De Luca D, Autilio C. Strategies to protect surfactant and enhance its activity. *Biomed J* 2021;44:654–62.
- [10] Autilio C. Techniques to evaluate surfactant activity for a personalized therapy of RDS neonates. *Biomed J* 2021;44:671–7.
- [11] Kitsioulis E, Nakos G, Lekka ME. Phospholipase A2 subclasses in acute respiratory distress syndrome. *Biochim Biophys Acta* 2009;1792:941–53.
- [12] De Luca D, Touqui L. The International Week of Surfactant Research: increasing knowledge about surfactant and unexploited opportunities. *Biomed J* 2021;44:651–3.
- [13] Murakami M, Taketomi Y. Secreted phospholipase A2 and mast cells. *Allergol Int* 2015;64:4–10.
- [14] Piroli ME, Blanchette JO, Jabbarzadeh E. Polarity as a physiological modulator of cell function. *Front Biosci (Landmark Ed)* 2019;24:451–62.
- [15] Rognon J, Peng X, Mostov K. Polarity in mammalian epithelial morphogenesis. *Cold Spring Harb Perspect Biol* 2013;5:a013789.
- [16] Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial–mesenchymal transition. *Nat Rev Mol Cell Biol* 2014;15:178–96.
- [17] Gonzalez DM, Medici D. Signaling mechanisms of the epithelial–mesenchymal transition. *Sci Signal* 2014;7:re8.
- [18] Niu H, Qu A, Guan C. Suppression of MGAT3 expression and the epithelial–mesenchymal transition of lung cancer cells by miR-188-5p. *Biomed J* 2021;44:678–85.
- [19] Capote T. *Music Chameleons*. 2nd ed. New York: Penguin; 2001. p. 58.
- [20] Stavrianos LS. *A global history: from prehistory to the present*. 5th ed. Englewood Cliffs, NJ.: PrenticeHall; 1991.
- [21] Trueba G, Dunthorn M. Many neglected tropical diseases may have originated in the paleolithic or before: new insights from genetics. *PLoS Negl Trop Dis* 2012;6:e1393.

- [22] Weyrich LS, Duchene S, Soubrier J, Arriola L, Llamas B, Breen J, et al. Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. *Nature* 2017;544:357–61.
- [23] Hardy K, Buckley S, Collins MJ, Estalrich A, Brothwell D, Copeland L, et al. Neanderthal medics? Evidence for food, cooking, and medicinal plants entrapped in dental calculus. *Naturwissenschaften* 2012;99:617–26.
- [24] Bracha HS, Person DA, Bernstein DM, Flaxman NA, Masukawa NK. Combat and warfare in the early paleolithic and medically unexplained musculo-facial pain in 21st century war veterans and active-duty military personnel. *Hawaii Dent J* 2005;36:16–8.
- [25] Peng HH, Huang PR, Young JD, Ojcius DM. Physical attributes of salivary calcium particles and their interaction with gingival epithelium. *Biomed J* 2021;44:686–93.
- [26] Yehya AHS, Asif M, AbdulMajid AMS, Oon CE. Complementary effects of *Orthosiphon stamineus* standardized ethanolic extract and rosmarinic acid in combination with gemcitabine on pancreatic cancer. *Biomed J* 2021;44:694–708.
- [27] Burris 3rd HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–13.
- [28] Amrutkar M, Gladhaug IP. Pancreatic cancer chemoresistance to gemcitabine. *Cancers (Basel)* 2017;9:157.
- [29] Chua LS, Lau CH, Chew CY, Ismail NIM, Soontornngun N. Phytochemical profile of *Orthosiphon aristatus* extracts after storage: rosmarinic acid and other caffeic acid derivatives. *Phytomedicine* 2018;39:49–55.
- [30] Braga FC. Brazilian traditional medicine: historical basis, features and potentialities for pharmaceutical development. *J Tradit Chin Med Sci* 2021;8:S44–50.
- [31] Malpezzi-Marinho ELA, Molska GR, Freire LIGP, Silva CI, Tamura EK, Berro LF, et al. Effects of hydroalcoholic extract of *Solidago chilensis* Meyen on nociception and hypernociception in rodents. *BMC Complement Altern Med* 2019;19:72.
- [32] Perez-Favila A, Martinez-Fierro ML, Rodriguez-Lazalde JG, Cid-Baez MA, Zamudio-Osuna MDJ, Martinez-Blanco MDR, et al. Current therapeutic strategies in diabetic foot ulcers. *Medicina (B Aires)* 2019;55:714.
- [33] Moreira JAR, Vasconcelos IC, Fachi JL, Theodoro V, Dalia RA, Aro AA, et al. Application of *Solidago chilensis* and laser improved the repair of burns in diabetic rats. *Biomed J* 2021:709–16.
- [34] Lee PC, Hsieh PH, Chou YC, Wu CC, Chen WJ. Dynamic hip screws for unstable intertrochanteric fractures in elderly patients—encouraging results with a cement augmentation technique. *J Trauma* 2010;68:954–64.
- [35] Chang FC, Chuang PY, Lee CY, Lee CY, Chou YC, Huang TW, et al. The effects of bone-substitute augmentation on treatment of osteoporotic intertrochanteric fractures. *Biomed J* 2021;44:717–26.
- [36] Wick JY. The history of benzodiazepines. *Consult Pharm* 2013;28:538–48.
- [37] Ramsey JT, Shropshire BC, Nagy TR, Chambers KD, Li Y, Korach KS, et al. Essential oils and health. *Yale J Biol Med* 2020;93:291–305.
- [38] Kwangjai J, Cheaha D, Manor R, Sa-ih N, Samerphob N, Issuriya A, et al. Modification of brain waves and sleep parameters by *Citrus reticulata* Blanco. cv. Sai-Nam-Phueng essential oil. *Biomed J* 2021;44:727–38.
- [39] Chang WH, Tu LW, Pei YC, Chen CK, Wang SH, Wong AM. Comparison of the effects between lasers applied to myofascial trigger points and to classical acupoints for patients with cervical myofascial pain syndrome. *Biomed J* 2021;44:739–47.
- [40] Kun YY, Chen FP, Chaung HL, Chou CT, Tsai YY, Hwang SJ. Evaluation of acupuncture effect to chronic myofascial pain syndrome in the cervical and upper back regions by the concept of Meridians. *Acupunct Electrother Res* 2001;26:195–202.
- [41] Chen CH, Huang YS, Fang TH. Identification of a novel nonsense homozygous mutation of *LINS1* gene in two sisters with intellectual disability, schizophrenia, and anxiety. *Biomed J* 2021;44:748–51.