Environmental Science and Ecotechnology 15 (2023) 100252

Contents lists available at ScienceDirect

Environmental Science and Ecotechnology

journal homepage: www.journals.elsevier.com/environmental-science-and-ecotechnology/

Review

Reimagining safe lithium applications in the living environment and its impacts on human, animal, and plant system

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ARTICLE INFO

Article history:
Received 5 August 2022
Received in revised form
8 February 2023
Accepted 13 February 2023

Keywords:
Lithium
Plants health
Soil ecology
Domestic and aquatic animals
Human health
Threshold levels

ABSTRACT

Lithium's (Li) ubiquitous distribution in the environment is a rising concern due to its rapid proliferation in the modern electronic industry. Li enigmatic entry into the terrestrial food chain raises many questions and uncertainties that may pose a grave threat to living biota. We examined the leverage existing published articles regarding advances in global Li resources, interplay with plants, and possible involvement with living organisms, especially humans and animals. Globally, Li concentration (<10 −300 mg kg^{-1}) is detected in agricultural soil, and their pollutant levels vary with space and time. High mobility of Li results in higher accumulation in plants, but the clear mechanisms and specific functions remain unknown. Our assessment reveals the causal relationship between Li level and biota health. For example, lower Li intake (<0.6 mM in serum) leads to mental disorders, while higher intake (>1.5 mM in serum) induces thyroid, stomach, kidney, and reproductive system dysfunctions in humans and animals. However, there is a serious knowledge gap regarding Li regulatory standards in environmental compartments, and mechanistic approaches to unveil its consequences are needed. Furthermore, aggressive efforts are required to define optimum levels of Li for the normal functioning of animals, plants, and humans. This review is designed to revitalize the current status of Li research and identify the key knowledge gaps to fight back against the mountainous challenges of Li during the recent digital revolution. Additionally, we propose pathways to overcome Li problems and develop a strategy for effective, safe, and acceptable applications.

1. Introduction

Lithium (Li), also known as white gold, is a key component of modern “green” batteries [1]. Globally, Li production reached 100,000 metric tons in 2021, a 256% increase from 2010 (USGS

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https://doi.org/10.1016/j.ese.2023.100252

2012–2022) (Fig. 1a and b), with 74% of it going into rechargeable Li-ion batteries powering electronic products and electric vehicles [2]. On the one hand, the soaring demand for Li has led to an exponential increase in its supply; on the other hand, electronic waste is increasingly contributing to soil contamination with Li^{+} ions or Li_2O [3]. Lubricating grease accounts for 4% of total Li industrial applications [4] and enters the environment through road runoff. Another 14% is used for ceramics and glass production and ends up in municipal waste/landfills (Fig. 1c) [5]. Even Li ingested by humans is excreted through the kidneys within 24 h and is discharged into sewage [6]. Highly variable concentrations of Li in the environment and food products have deleterious effects on animal and human health [7,8] and represent a growing challenge for regulators.

Li is a non-essential micronutrient, but its deficiency causes aggressive behavior, suicidal tendencies, bipolar or unipolar disorder, and acute mania. Li deficiency alters milk production and reproduction patterns in domestic animals [9]. The exact mechanism explaining such events remains unclear. When present at high doses (approximately 17.5–24 mg L^{-1}) in the blood, Li induces visual nausea, impairment, and kidney problems; while beyond 24 mg L^{-1}, it causes cardiac arrest and coma [10]. LiCl toxicity has directly affected testicular tissue function, leading to male infertility via impaired steroidogenesis and spermatogenesis [11]. Li accumulates in the brain, gills, and kidneys of fish, which may represent a risk to the food chain [12]. The Li concentration in the plants usually lies between 0.2 and 30 mg kg^{-1} due to preferential uptake or exclusion across species. The bioaccumulation of Li depends on the plant species and the location where they are cultivated [13]. Thibon et al. [12] reported Li accumulation in the brain (0.34 mg kg^{-1}), gills (0.26 mg kg^{-1}), kidneys (0.15 mg kg^{-1}), liver (0.07 mg kg^{-1}), and muscles (0.06 mg kg^{-1}) of fish species. Furthermore, the amount of Li in the normal human body is approximately 7.0 mg [14]. Various reports regarding the role of Li in biological systems call for uniform safety standards in living organisms. To this end, recent studies have described the current supply of Li [15], Li flux in soil and water following remediation strategies [7], the benefits and dietary intake of Li, and the role of Li in crops [16,17]. Bolan et al. [18] briefly overviewed the potential effects of higher Li levels in living organisms.

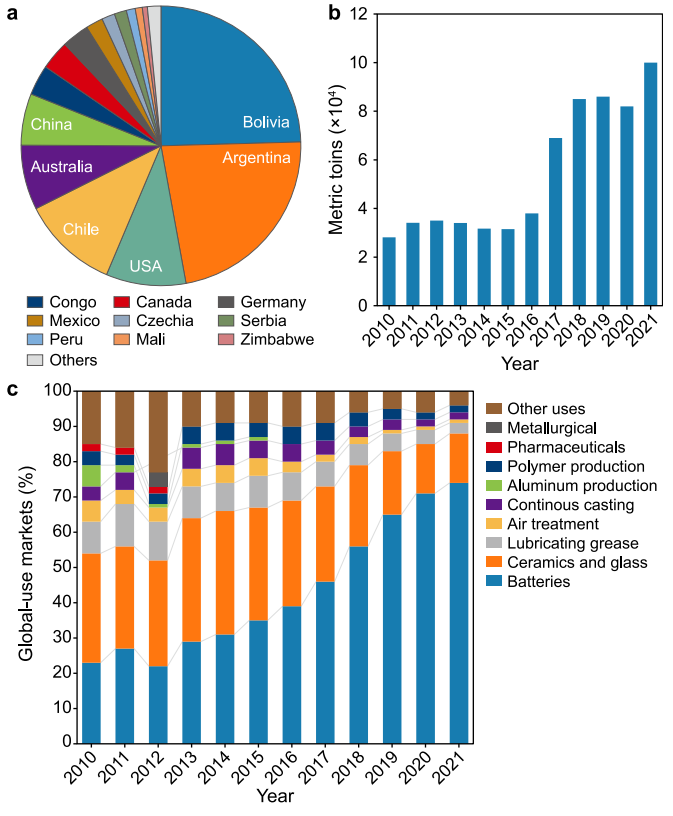

Fig. 1. **a**, Total Li resources by different countries (metric tons) in 2020. **b**, Global production of Li from mining for the period 2010–2020. **c**, Global market consumption (%) over the last ten years [4,19–21].

Despite considerable progress, exposure to critical concentrations of Li and the associated health risks remain poorly explored. First, the abundance of Li in different environmental compartments should be compared. Second, a comprehensive framework addressing the effect of Li on humans and animals should be produced.

This review emphasizes the impact of Li on soil, plant, animal, and human health, highlighting areas of interest for investigators from the life sciences and environmental research fields. This study addresses the natural and anthropogenic sources, consumption, fate, and speciation of Li. For every environmental compartment, the study identifies the key gaps that should be filled by future research. In particular, the review discusses the interaction of Li with animals and humans, as well as the beneficial and toxic effects of a daily intake of Li. A final section points to the emerging uses of Li in modern digital devices and a future roadmap aimed at minimizing the lethal consequences of Li in living organisms, thus ensuring more sustainable growth.

2. Accumulation and transport of Li in the soil

The level of Li in the soil varies greatly based on the mineral type and rock composition, the presence of authigenic minerals generated during alkaline-acid redox processes, and the occurrence of hypergenesis regions [8]. The concentration of Li in different agricultural soils has been reported at 0.01–160 mg kg^{-1} [19] and 7–200 mg kg^{-1} [20] (Table S1). In China (Beijing), contamination with Li in agricultural soils ranges between 17.11 and 38.50 mg kg^{-1} [21] (Fig. 2). Soils in northern Europe have relatively low Li content (median 6.4 mg kg^{-1}), whereas those in southern Europe have more Li (median 15 mg kg^{-1}) [22]. In Romania, Li content varies from 7 to 200 mg kg^{-1} [23,24]. Additionally, the accumulation of Li depends on soil pH, with acidic soils promoting Li solubility and resulting in higher Li content [10]. Several Li fractions are integrated into sediment and soil components, each characterized by a different interaction pattern and mobility [25]. Li found in soil and sediment matrices forms exchangeable (primarily carbonate-phase), reducible (Mn/Fe hydroxides), oxidizable (organic matter and sulfides), and residual fractions (silicate phases) [26]. Exchangeable fractions have the lowest Li concentration (2%), whereas residual fractions have the highest (59–84%) [27]. Reducible and oxidizable fractions account for 3–28% and 1–5% of total Li, respectively. Li is readily absorbed by plants, from which it enters the food chain [10]. Some countries report elevated Li brine levels, but no data are available for agricultural soils (Table S1).

3. Fate and speciation of Li in the soil

The fate of Li depends on the soil's physical characteristics, such as bulk density, texture, color, and permeability [28]. Li accumulation is regulated by clay concentration and the background Li content of the parental material [29]. Clay fractions contain substantially more Li than organic fractions, and the topsoil harbors less Li than the underlying layers [20]. During oxidation processes, Li is released from the parental material into clay soil, which is fixed by mineral oxides or organic matter before eventually

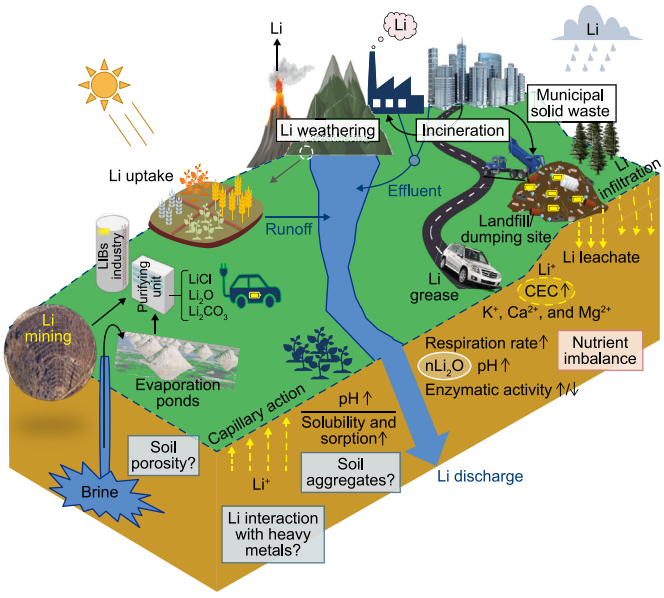

Fig. 2. Overview of natural and anthropogenic sources of Li in the soil, together with the fate and speciation of Li ions. Upward pointing arrows (↑) indicate high levels or increases, downward pointing arrows (↓) indicate low levels or decreases, dotted arrows indicate the movement of Li caused by various environmental factors, and the dotted circle denotes the replacement of cations with Li (cation exchange capacity), and the question mark (?) highlights existing knowledge gaps.

accumulating in phosphate rocks [7]. A positive relationship was observed between exchangeable Li in the soil and soil clay concentration; however, an inverse relationship exists between water-soluble Li and clay content [30]. In Piedmont soils, a weak but significant correlation (r^2 = 0.623) was detected between exchangeable Li and clay. During the weathering of aluminosilicates, the concentration of Li becomes proportional to that of Mg due to similarities in their ionic radii and weak coordination with major ions. Indeed, Li can efficiently replace other metal ions, such as K^+, Na^+, Mg^{2+}, and Ca^{2+}, because of its high affinity for clay, similar radius, and comparable polarizing strength [31,32]. Moreover, rare elements can associate with minerals in solid solutions, within inclusion products, in structural cavities or voids, in an adsorbed phase, and as mechanically admixed impurities [7]. Soils rich in clay tend to have higher cation exchange capacity [33], which enhances the availability of Li but lowers that of essential minerals (Fig. 2). The availability of Li in the soil is influenced by pH [8], with low pH having a positive effect. A high concentration of Li significantly enhances soil electrical conductivity [34]. Moreover, Li content is influenced by the amount of organic matter, which acts as a key sorbent for Li in forest soils. Even in highly Li-contaminated soils, organic input from manure, compost, bio-solid waste, and crop residues can significantly minimize the availability of Li to plants [35]. Finally, Li accumulation is influenced by climate. In arid regions, solubilized Li follows an upward movement and may precipitate within the top soil strata along with easily soluble sulfates, chlorites, and borates. The high amount of Li in such soils (e.g., solonetz, solonchaks, prairie, and kastanozems) favors chemical reactions. In humid climatic zones, Li leaches down easily through the soil profile [36] (Fig. 2).

Li bioavailability is greater in acidic than alkaline soils due to enhanced Li solubility and fewer chances to form Li-ligand complexes by chaperones [35]. The scarcity of binding sites for cations in acidic soil, a less negative surface charge, and enhanced solubility of Li may contribute to higher Li absorption by plant tissues [34].

Ionic strength, soil exchange sites, root surface exchange sites, and the presence of other ions have a strong impact on Li uptake [27]. Ionic activity in growth medium has an inverse relationship with Li availability and the content of trace metals in plants [37]. Root exudates are secondary products of photosynthesis; they include polysaccharides, sugars, amino acids, peptides, proteins, and organic acids [38]. In particular, citric acid and malic acid protect plant roots from Li toxicity by binding and sequestering the metal [10]. Future research should focus on the role of rhizosphere microbial communities in the sustainable regulation of Li bioavailability within soil ecosystems and assess it in relation to soil pH, bulk density, texture, composition, organic matter, and root exudates in both acidic and alkaline soils.

4. Role of Li in soil ecology

4.1. Response of soil invertebrates to Li

Geochemically, Li is a highly mobile element, which implies an elevated environmental and occupational health and safety risk [14]. Certain Li compounds are biologically relevant, although their toxicity on living organisms is poorly documented [7]. Exposure of the ramshorn snail (*Planorbis rubrum)* and giant ramshorn snail (*Marisa cornuarietis*) to 50–5000 μg L^{-1} LiCl for seven days was shown to alter epithelial and mucous cells of the epidermis, change basophilic cells, cause irregularly shaped cilia, produce abnormal apices of digestive cells, vary the amount of mucus in the gills, and lead to deleterious swelling of hepatopancreatic digestive cells. The EC_{50} values of LiCl in the epidermis, digestive cells, basophilic cells, apex, and gills of *M. cornuarietis* were 2523.9, 220.8, 967.6, 231.8, and 1402.5 μg L^{-1}, respectively [39]. Tam et al. (2014) reported a 10% increase in the lifespan of the nematode *Caenorhabditis elegans* following 10 mM LiCl exposure [40]. Treating *C. elegans* with LiCl (156–1000 μM) and Li_2CO_3 (47–3000 μM) for 55 h decreased the body length at >1250 μM LiCl or >750 μM Li_2CO_3 and significantly decreased the number of offspring by 37–85% at 500–1000 μM LiCl and by 10–72% at 1500–3000 μM Li_2CO_3 [41] (Fig. 3).

The amount of mitochondrial DNA in *C. elegans* was found to increase significantly (12%) after 24-h exposure to 10 mM LiCl but then dropped on day 8 (13%) and 14 (31%) compared to the control [40]. Growth in medium containing 312–5000 μM LiCl or 750–3000 μM Li_2CO_3 was shown to alter the expression of genes related to cytochrome P450 (36 genes), glutathione S-transferase (ten genes), lipid metabolism (16 genes), ABC transporter (16 genes), and vitellogenin (two genes), which points to the potential effect of Li on biological and physiological functions in *C. elegans* [41]. Meisel and Kim [42] reported that 15 mM LiCl inhibited phosphatase bisphosphate 3-nucleotidase in the nervous system of *C. elegans*, resulting in selective dysfunction of ASJ chemosensory neurons and causing selective toxicity to specific neurons on the fourth day of exposure (Fig. 3). Surprisingly, Fischer and Molnar (1997) reported that 1 mg kg^{-1} LiCl induced a significant drop in body weight (50%), while 10 mg kg^{-1} LiCl halved the survival rate of the earthworm *Eisenia fetida* after 49 days of exposure when the LC_{50} was 70 mg kg^{-1} [43]. The effect of Li on the nervous system and the underlying toxicity mechanism require comprehensive investigations in large organisms such as *C. elegans* and earthworms.

4.2. Response of soil microbes to Li

Microbes are major players in terrestrial ecosystems because they are vital in soil ecology and involvement in different biogeochemical carbon and nutrient cycles. Porter and Bernot [44] investigated the effects of Li (0.05–10 mg L^{-1}) on microbial activity and found that increasing the Li concentration reduced the respiration rate (8–27%) in microorganisms, while no effect was

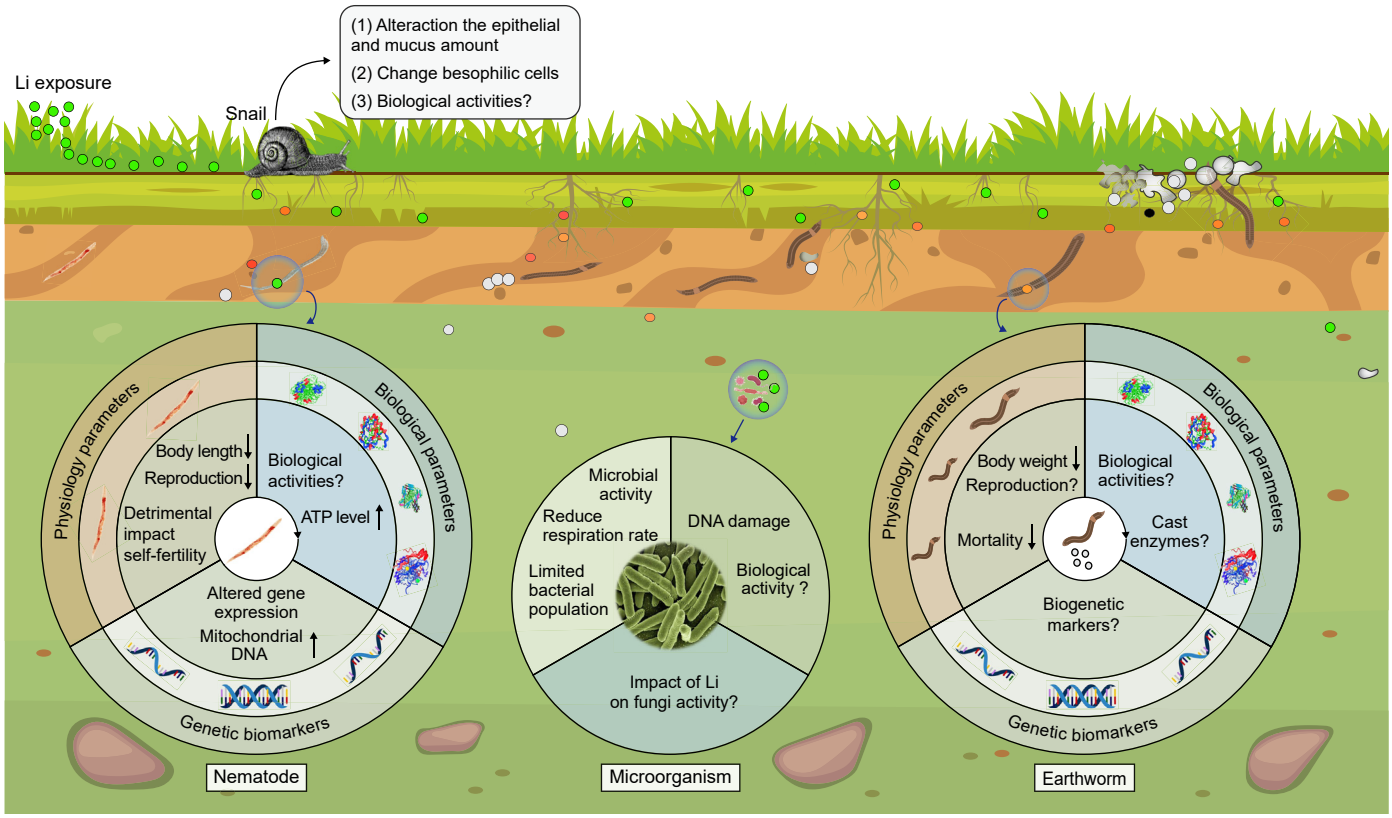

Fig. 3. Schematic representation of the harmful effects of Li on macroorganisms (earthworms, nematodes, and snails) and microorganisms in the soil environment. Upward pointing arrows (↑) indicate an increase, downward pointing arrows (↓) indicate a decrease, and the question mark (?) highlights existing knowledge gaps.

observed on nitrate and phosphate uptake at the highest (5 or 10 mg L^{-1}) exposure levels. Reduced microbial activity in the soil might limit bacterial production, which in turn would destabilize the food chain and alter biogeochemical cycles.

Avila-Arias et al. [3] reported a 30–45% reduction in soil DNA, a 25–100% reduction in β-glucosidase activity, and a 28–50% increase in urease activity following exposure to Li_2O-nanoparticles at 51 and 474 mg kg^{-1}. Another study reported the effect of 5 mg L^{-1} $Li_{1/3}Ni_{1/3}Mn_{1/3}Co_{1/3}O_2$ nanoparticles on metabolic respiration and a 109% increase in DNA damage in the gram-positive bacterium *Bacillus subtilis* [45].

Recently, the toxic effect of Li on sorghum (*Sorghum vulgare*) was found to be offset by the application of Li-resistant bacteria (*Bacillus velezensis*) to soil contaminated with 50–100 mg kg^{-1} LiCl. As a result, the number of leaves increased by 10–15% in plants grown in bacteria-treated soil compared to those from non-treated soil [46]. More studies are required to identify bacterial mechanisms responsible for reducing Li toxicity and possibly mitigate the detrimental impact of Li on the soil environment. Overproduction of reactive oxygen species, proteins, and enzyme malfunction; destruction of thiol and iron-sulfide clusters; Li substitution and obstruction of food uptake; lipid peroxidation; and DNA damage are all harmful responses caused by an excess of Li in microbial cells. As a result of toxicity, microorganisms and the microbial community suffer irreversible harm due to mutagenicity and/or cell death.

5. Lithium in air

Lithium is flammable metal and potentially explosive when suddenly exposed to air [47]. Airborne dust clouds of Li (LiOH) may explode in contact with heat. In the presence of moisture, Li hexafluoroarsenate has the potential to form hydrogen fluoride, a highly corrosive gas [47]. However, there is negligible inhalation of Li from the air as ambient air levels are low (2–4 ng m^{-3}), but it depends on the location. Such as, mining companies take 750 tons of brine to produce 1.0-ton Li [48]. In places where Li brines crystallize by evaporation, the Li content of the air could be higher [47]. Furthermore, Li enters the atmosphere through fly ash particles that are generated by the combustion of coals. The average Li concentration in the global coals is estimated to be 12 mg kg^{-1} [49], with the highest concentration (31.8 mg kg^{-1}) of Li in China coals [50], followed by the United States (16 mg kg^{-1}) [51]. Schlesinger et al. estimated the Li concentrations in the coal combustion residuals, which was 372 mg kg^{-1} [51,52]. Previous studies documented the release of fly ash particles into the atmosphere and deposition on surface soils [52–54]. Schlesinger et al. estimated that 10% of the Li in coal combustion residues was released to the atmosphere in particles forms, inferring a global Li flux of 55×10^9 g $year^{-1}$ in 2019 (i.e., 10% of the Li flux from coal combustion escapes as fly ash aerosols) [52]. On the other hand, during the recycling process of LIBs, fine particles are released into the air system. These fine particles could cause deleterious effects on the respiratory system of workers in recycling areas [55]. Furthermore, other chemicals (e.g., PAHs) released from the recycled batteries may deposit together in the atmosphere [56]. There are no details studies regarding Li aggregates and deposition in the air during extraction and mining. As demand increases, Li extraction may cause air pollution, and it is urgently needed to assess its possible toxic effects on the respiratory system.

6. Uptake, accumulation, and translocation of Li in plants

Roots are the major point for Li uptake by plants. According to

one hypothesis, Li enters the root system through the apoplast, is transported to the cells through the cell wall, and may reach the xylem through a partially open Casparian strip. According to a second hypothesis, Li enters the roots via transpirational pull under a high Li concentration [27] (Fig. 4), followed by passive entry through cation transporters into the endodermis of root hair cells and further diffusion to adjacent cells via plasmodesmata [57].

In the case of Li stress, several transporters, such as low-affinity cation transporter, non-selective cation channel (NSCC), and high-affinity K^+ transporter, participate in Li intake [58]. After entry into root cells with the help of transporters, Li accumulates in the cytosol and then enters the xylem, from where it reaches the leaves. Under Li toxicity, NSCCs are activated either by decreased cytosolic Ca^{2+} or higher cytosolic reactive oxygen species, which help translocate Li from the apoplast to the above-ground portion via the cytosol. Based on the transport of other metals (Ca^{2+}, K^+, and Na^+), it is believed that Li uptake occurs via the NSCC-mediated symplast pathway. As it can substitute Ca^{2+} and K^+, Li enters the cell via passive conductance [59] (Fig. 4).

Whether the translocation of Li to the leaves and shoots occurs via the xylem or phloem remains unknown [27]. Hawrylak-Nowak et al. [60] reported higher Li accumulation in hydroponically grown sunflower shoots (3292 mg kg^{-1}) compared to maize shoots (695 mg kg^{-1}) when exposed to 50 mg L^{-1} Li. Furthermore, Antonkiewicz et al. (2017) documented higher Li accumulation in maize roots (1211–1733 mg kg^{-1}) than in other plant parts (114–356 mg kg^{-1} in the stem and 111–408 mg kg^{-1} in the leaves) when grown in Li-contaminated nutrient solution (32–64 mg L^{-1}) [61]. When leaves of the pine *Podocarpus macrophyllus* were dipped in 1000 mg L^{-1} LiCl for 8, 16, 24, and 48 h, an elevated Li concentration (1000 ppm) was noted on the edges of leaves compared to midribs [62], suggesting that the xylem and not the phloem carried Li from the roots to the shoots. Furthermore, the accumulation of Li appeared to depend on its concentration in the soil, as well as the type of plant part and the translocation factor.

Once it is translocated to the shoots, Li must be stored in different cell organelles, determining its tolerance. Li compartmentalization is an important indicator of its tolerance. Li-accumulating species such as the sword-leaf dogbane *Apocynum*

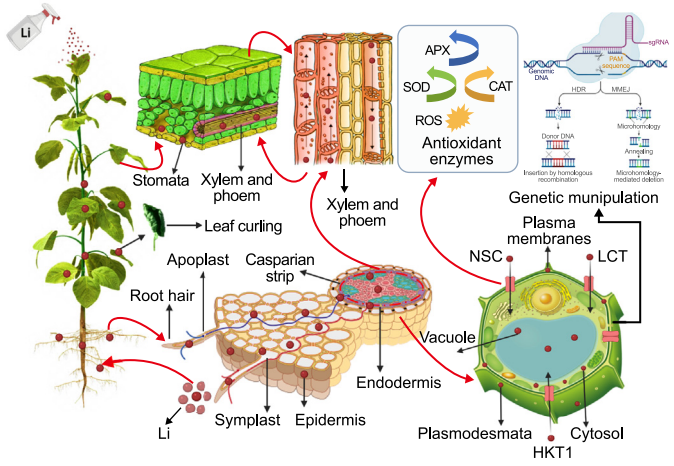

Fig. 4. Mechanism of Li uptake and transport from root cells to shoots and Li sequestration in plant cells. Li enters root cells via the symplast or apoplast pathway. In the symplast pathway, various cation transporters, such as low-affinity cation transporter 1 (LCT1), non-selective cation channel (NSCC), and high-affinity K^+ transporter 1 (HKT1) present in the plasma membrane, may assist in taking up and transporting Li to the xylem. NSCC is activated by reactive oxygen species (ROS), whose accumulation is induced by Li toxicity, but is restrained by the activity of antioxidant enzymes, such as ascorbate peroxidase (APX), catalase (CAT), and superoxide dismutase (SOD).

venetum can tolerate up to 25 mg L^{-1} LiCl, which corresponds to 72% of the total Li content in this species [63–65]. Jiang et al. [66] reported a positive correlation between Li accumulation in the leaves of *A. venetum* and soil Li concentrations (50–400 mg kg^{-1}). *A. venetum* may be employed as a model organism for investigating Li activity in plant systems. Qiao et al. [63] found that the highest amount of Li was detected in the soluble fraction (45–72%), followed by the cell wall (14–29%), plastid (4–12%), nucleus (4–9%), and mitochondria (1–4%) of *A. venetum* cultivated in hydroponic medium with 25 mg L^{-1} LiCl. However, the force driving the movement of Li from the cytosol to the vacuole remains unknown, pointing to the need for further studies on the accumulation of Li at the subcellular level.

6.1. Effect of Li on plant growth and development

While it is not an essential mineral for plants, Li affects the growth and metabolism of some halophytes. Its accumulation in plants is dictated by the concentration of Li ions in the soil, as indicated by the different intensity of curling and necrotic lesions in tobacco (*Nicotiana tabacum*) when exposed to 15–50 mM LiCl in hydroponic medium and overall toxicity >50 mM LiCl [67]. Kavanagh et al. [68] grew 34 *Brassica* species in Li-contaminated soils (20–1000 mg L^{-1}) to investigate Li accumulation. An initial screening revealed more than 90% germination in nine species, with *Brassica napus* and *Brassica oleracea* accumulating the most Li (2590 and 3091 mg kg^{-1}). Accordingly, it was proposed that 1 ton of plant biomass might yield 0.26 kg of Li [68]. Li et al. [69] observed faster growth of *Brassica carinata* seedlings <60 mM Li but a significant decrease (40–80%) in chlorophyll content and retarded growth >60 mM. Hawrylak-Nowak et al. [60] investigated the effect of 2.5–100 mg L^{-1} LiCl or LiOH on lettuce (*Lactuca sativa*) plants and found that shoot and root biomass were significantly higher (62%) with 2.5 mg L^{-1} LiOH, but significantly lower with 20–50 mg L^{-1} LiOH (19–69%) and LiCl (13–58%); whereas 100 mg L^{-1} completely inhibited growth.

Given the steadily growing Li contamination of soils, the need for natural Li remediation is becoming increasingly appealing. Jiang et al. [70] reported that *A. venetum* offered an excellent phytoremediation solution for Li-contaminated soils, as 10 and 15 mg kg^{-1} LiCl significantly increased the dry weight of leaves (24–33%), stem (20–26%), and root (29–44%). However, these increments were limited at higher doses (20 and 25 mg kg^{-1}). Foliar application of Li enhanced soybean grain yield by 10.73% at 45.7 mg kg^{-1} Li_2SO_4 but reduced it by 20% at 120 mg kg^{-1} Li_2SO_4 and by 49% at 120 mg kg^{-1} LiOH [71]. Furthermore, foliar spraying of 10–40 mg kg^{-1} LiOH and Li_2SO_4 increased lettuce root dry weight by 31% and 18%, respectively, at lower to medium concentrations (20 and 30 mg kg^{-1}), while at 40 mg kg^{-1}, a significant reduction (22%) was noted [72] (Table 1). Hence, it can be concluded that, at higher amounts, Li exerts a species- and plant-part-specific negative impact on plant physiological responses and growth. More studies are needed to understand the mechanism of Li toxicity at high concentrations and how transmembrane transport may contribute to it. In addition, long-term studies should explore the changes in plant physiology and its nutritional composition, especially in vegetables, Li-accumulating *Brassica* spp., and leguminous bean crops.

6.2. Response of biochemical indicators to Li exposure

Li contamination may impose stress on plant signaling and metabolic pathways. Orbán and Bóka (2013) reported the formation of H_2O_2 in rose madder (*Rubia tinctorum*) cell cultures after treatment with 1 and 20 mM LiCl over a varying time period (0–240 min). Importantly, pre-treatment with *botrytis* caused a

large difference in H_2O_2 formation between 1 mM Li (22 mg g^{-1}) and 20 mM Li (28 mg g^{-1}) after 240 min [73]. Exposure of spinach (*Spinacia oleracea*) to 20–80 mg kg^{-1} LiCl significantly improved the antioxidant activity of superoxide dismutase (19–35%), catalase (27–39%), and ascorbate peroxidase (131–182%), together with an increase in H_2O_2 release and lipid peroxidation [74] (Table 1). Sorghum plants exposed to increasing concentrations of LiCl (0, 10, 50, and 100 mM) exhibited an enhanced synthesis and consequent activity of phosphoenolpyruvate carboxylase, whose phosphorylation decreased from 115 to 90, 53, and 0 mU, respectively [75]. Li et al. [69] exposed brown-seeded *B. carinata* to 60 mM Li and used microarray analysis to quantify the upregulation of genes encoding for GDSL-lipases (5-fold), lipid transfer protein-4 (5-fold), lipoxygenases (20-fold), protein precursor PR (29-fold), allene oxide synthase (2.9-fold), and O-methyltransferase (20-fold). Li exposure for 1–4 weeks was found to be also involved in the up/down-regulation of several genes of *Arabidopsis thaliana* involved in photosynthesis, respiration, and DNA/RNA synthesis. Interestingly, two genes not previously associated with Li stress were found to be downregulated (AtFBA5) and upregulated (AtGLP9) in response to acute Li^+ exposure, phenocopying Mg^{2+} deficiency, and affecting cell wall integrity [76].

7. Impact of Li on animals

7.1. Domestic animals

Feed and water are the main sources of Li in animals. The requirement for Li has been investigated in cows, goats, and rats. The Li limit in goats and pigs was found to be <2.5 mg kg^{-1} of dry matter [77]. A long-term study (15 years) to elucidate the influence of Li-deficient feed on pre- and postnatal growth of goats (*Capra hircus*) revealed that Li-deficient goats displayed 11% lower feed intake and 9% lower birth weight compared to control goats [9]. Moreover, 41% of Li-deficient goats died during the first year of the study, as opposed to 7% among control animals. Li-deficient goats gave birth to more female offspring, produced 20% less milk, and the conception rate on first mating was significantly lower. Whereas Li deficiency in goats did not affect the blood biochemical profile, it reduced the activity of several serum enzymes participating in the tricarboxylic acid cycle, including malate dehydrogenase, isocitrate dehydrogenase, aldolase, and glutamate dehydrogenase. Only creatine kinase activity was higher in Li-deficient goats. Monoamine oxidase, involved in manic disorders, presented 28% lower activity in Li-deficient goats [9] (Table 2).

Li can accumulate in animals through the food chain, with high concentrations causing severe damage [27]. For instance, a dose of 500–700 mg kg^{-1} led to severe depression and ataxia in mixed-breed beef cattle (*Bos taurus*), as well as residual Li in muscles (86.64 mg L^{-1}), kidneys (66.97 mg L^{-1}), liver (68.57 mg L^{-1}), heart (79.15 mg L^{-1}), and brain (51.7 mg L^{-1}) tissues [78]. At the same time, the antiviral activity of LiCl against transmissible gastroenteritis virus, infectious bronchitis virus, pseudorabies herpesvirus, and enterovirus-A71 has been reported [79]. Injection with 25 mg kg^{-1} Li_2CO_3 twice a day for 30 days in Wistar rats (*Rattus norvegicus*) decreased testes weight, accessory sex organ size, sperm count, sperm motility, and serum testosterone levels while increasing lipid peroxidation due to decreased glutathione peroxidase, catalase, and superoxide dismutase activities in the testes [80]. Li_2CO_3 treatment significantly increased lipid peroxidation (53%) in rats fed a protein-deficient (8%) diet compared to those given a high-protein (30%) diet, in which the increase was only 18% [20]. According to Aral and Vecchio-Sadus (2008), the LC_{50} value of LiCl for rats ranged from 526 to 840 mg kg^{-1}. Longer exposure to high Li doses has been found to induce weight gain and polydipsia, damage to the male reproductive system, a significant reduction in plasma testosterone levels, and oxidative stress in the liver [81] (Table 2).

The addition of 20 mg kg^{-1} LiCl was not reported to have any negative effect on weight gain and meat quality of broiler chickens; however, it led to 22% lower stiffness of the femur (long bone) but no alteration to the toughness of the tibia [82]. LiCl overload (100 mg kg^{-1}) affected glucose metabolism in broiler chickens, increasing the expression of the glucose transporter GLUT-3 and GLUT-9 in the liver, as well as GLUT-1, GLUT-3, GLUT-8, and GLUT-9 in the pectoralis major muscle, cytosolic phosphoenolpyruvate carboxykinase (PEPCK) in the liver and mitochondrial PEPCK in the pectoralis major muscle. As a result, glucose tolerance and

Table 1
Impact of various sources of Li salts and concentrations on plant health.

Li source	Concentration (mg L^{-1})	Plant species	Duration (days)	Plant response	Reference
LiCl	0, 5, 25, 50	*Zea mays* L. var. *saccharata* Kcke & *Helianthus annuus* L.	14	Fresh shoots and roots biomass ↓, leaf areas ↓, photosynthetic pigment ↓, MDA ↓, potassium contents ±.	[99]
LiCl, LiOH	0, 2.5, 20, 50, 100	*Lactuca sativa* var. *capitata*	21	Fresh shoots and roots biomass ↓, necrotic spots on older leaves, L-Ascorbic acid ↓, water content ↓.	[100]
LiCl	0, 50, 200, 400	*Apocynum venetum*	28	Dry biomass ↓, photosynthetic pigments and parameters ↓.	[101]
LiCl	0, 25, 50, 200, 400*	*Apocynum pictum*	90	Germination ↓, Dry leaf, shoots, and roots biomass ↓, photosynthetic pigments ↓, soluble sugar content ↑, proline content ↑.	[102]
LiCl	0, 10, 15, 20, 25	*Apocynum venetum*	90	Dry leaf, shoot, and root biomass ↑, hyperoside content ↑, rutin content ↑, total flavonoids ↑.	[70]
LiOH	0, 10, 20, 30, 40◦	*Lactuca sativa* L.	40	Plant height ↓, Dry leaves and shoot biomass ↓, stem diameter ↓.	[72]
Li_2SO_4	0, 10, 20, 30, 40◦	*Lactuca sativa* L.	40	Stem diameter ↑, shoot/root ratio ↑,	[72]
LiCl.H_2O	0, 20, 40, 60, 80*	*Spinacia oleracea*	140	Shoot and root dry biomass ↑, chlorophyll pigments ↑, H_2O_2 and MDA ↑.	[74]
LiCl	0, 50, 100, 150, 200	*Sorghum vulgare* Pers.	150	Number of leaves ↓, plant height ↓, photosynthetic parameters ↓, shoot and root fresh biomass ↓.	[46]
LiCl	0, 50, 100, 150, 200#	*Sorghum vulgare* Pers.	150	Number of leaves ↑, plant height ↑, photosynthetic pigments and parameters ↑, shoot and root fresh biomass ↑.	[46]
Li_2O	0, 25, 50, 100, 200*	*Glycine max*	28	Shoot and root fresh biomass ↓, photosynthetic pigments and parameters ↓, numbers of nodules ↓, antioxidant activity ↓, metabolic activity ↓.	[17]

Note: H_2O_2: hydrogen peroxide; MDA: malondialdehyde. "↑": increase; "↓": decrease; "±": mixed effect; "*": the concentration of Li in the soil medium; "◦": foliar application of Li; "#": the application of Li with bacteria (*Bacillus velezensis*).

Table 2
Impact of Li on domestic animals and aquatic or semiaquatic species.

Species	Li concentration (mg per kg BW)	Li type	Duration (day)	Findings	References
Cattle and sheep	10, 20, 30, 40 mM	LiCl	1	Inhibited replication of foot-and-mouth disease-causing viruses.	[103],
Goat	1.7 and 2.5 (deficiency)			Body weight ↓; milk ↓; life expectancy ↓; ICDH, MDA, GLDH, and glycolysis ↓; creatine kinase activity ↑.	[9]
Rat (albino Wistar)	15–30	LiCl	49	Alanine and aspartate transaminases ↓, glutathione ↓, lipid peroxidation ↑, oxidative stress in red blood cells, liver and kidney tissues deformities.	[104]
Rat (Sprague-Dawley)	800	Li	1	Locomotion ↓, rearing ↓, anxiety ↑, impaired memory, and brain acute chronic poisoning.	[105]
Rat (Wistar)	1 mM kg^{-1} day^{-1}	[106,107] [106,107]	28 28	Oxidative-nitrosative stress ↑, stimulated nuclear translocation of nuclear factor erythroid-2-related factor 2, phosphoinositide 3-kinase activity ↓, protection against ventricular arrhythmias, HSP70 ↓.	[106,107]
Rat (albino)	100 mg kg^{-1} day^{-1}	Li_2CO_3 LiCl	28 21	MDA, creatinine, and neuron-specific enolase ↑; testosterone, superoxide dismutase, and glutathione ↓; massive loss of sperm atonic cells.	[108]
Rat (albino Wistar)	20 mg kg^{-1} day^{-1}	$LiNO_3$	49	Serum Ca and P ↑, alkaline and acid phosphate ↑, kidney tissues deformation, necrosis, binucleated cells and Kupffer cells visible in renal tissue, toxicity induction.	[109]
Mice (Kunming)	25	LiCl	14	Hippocampal neurogenesis ↓, p-GSK-3b level ↓, ACR-induced neuropathy.	[110]
Guinea pig ileum	1 mM LiCl	Li	4 h	Inhibited development of cannabinoid-induced tolerance and restored ileum sensitivity to the inhibitory action of WIN 55,212-2.	[111]
Broiler chickens	20 mg kg^{-1} day^{-1}	LiCl	1	Stiffness in the femur 22% ↓, energy-to-fracture of the tibia 32.6%↓, Li in serum ↑.	[82]
Chicken	120	LiCl	12	Detour learning ↑, brain-derived neurotrophic factor mRNA ↑.	[112]
Chicken embryo	5, 10, 20, 30 mM	LiCl	1–4	Inhibition of Newcastle disease-causing virus, protection from endoplasmic reticulum stress.	[84],

Note: BW, body weight; ICDH, isocitrate dehydrogenase; MDH, malate dehydrogenase; GLDH, glutamate dehydrogenase; HSP70, heat shock protein 70; MDA, malondialdehyde; "↑" indicate the increase; "↓" shows decrease.

gluconeogenesis were decreased, while insulin sensitivity and glucose transport were increased [83]. A Li-rich diet was found to decrease the transcriptional expression of preadipocyte proliferation markers, while a significant role of hypothalamic neuropeptide Y was recorded during adipogenesis in adipose tissues [83]. Treatment with 5–30 mM LiCl protects the cells from endoplasmic reticulum stress induced by Newcastle disease virus infection in chicken (*Gallus gallus domesticus*) [84] (Table 2). More studies on the beneficial and toxic effects of Li in these complex biological systems, as well as the function of Li as a viral inhibitor, are required.

7.2. Aquatic animals

The natural concentration of Li in surface waters is often <0.04 mg L^{-1} [85]. Mineral water contains 0.05–1.0 mg L^{-1} Li, although it may reach 100 mg L^{-1} in some cases [20]. Li does not have any harmful effects on aquatic life at low concentrations [86] but has a negative impact at a higher level. For example, exposure of zebrafish (*Danio rerio*) to 5–10 mg L^{-1} LiCl reduced adenosine diphosphate, whereas acetylcholinesterase and ecto-5-nucleotidase activities were decreased only at 10 mg L^{-1} LiCl [87]. Exposure of juvenile rainbow trout (*Oncorhynchus mykiss*) to 66 μg L^{-1} LiCl for nine days and 528 μg L^{-1} LiCl for the next six days in freshwater decreased plasma osmolality from 288 to 280 mosmol kg^{-1}, increased plasma Na^+ and K^+ from 143 to 168 mM L^{-1}, and decreased plasma Cl^- from 130 to 127 mM L^{-1}. Li did not affect free fatty acids and cholesterol in the trout blood plasma and gill tissues [88]. Thibon et al. [12] reported Li accumulation in the brain (0.34 mg kg^{-1}), gills (0.26 mg kg^{-1}), kidneys (0.15 mg kg^{-1}), liver (0.07 mg kg^{-1}), and muscles (0.06 mg kg^{-1}) of fish species. LiOH (30 mg L^{-1}) completely inhibited the movement of the water flea *Daphnia magna* within 24 h, with EC_{50} estimated at 12.58 mg L^{-1} [89]. Additionally, 10 and 20 mM LiCl was shown to promote the circadian period in zebrafish by 0.7 h [90], whereas 0.15 M LiCl was found to cause defects in eye development in zebrafish embryos, including lateral delay in eye formation, irregular eye shape, and loss of one eye [91]. Furthermore, at 0.30 M LiCl, embryos failed to develop the eyes altogether, and all embryos died at 0.45 M LiCl.

Selderslaghs et al. [92] have observed no teratogenic effect of 0.05 mM Li in zebrafish 48 h after fertilization. However, harmful effects, such as delayed development, skeletal deformities, dorsal curvature, reduced swimming, decreased heart rate, and decreased velocity, were observed in zebrafish at higher doses (235.9 mM) of LiCl [93]. A high concentration of Li causes a significant release of domoic acid in aquatic species, which affects embryonic development and causes microcephaly. Microcephaly caused by Li toxicity was also observed by treating salamanders (*Ambystoma punctatum* and *Ambystoma tigrinum*) and several frog species (including *Rana clamitans*, *Rana sylvatica*, *Rana catesbeiana*, and *Rana pipiens*) with 0.17–0.7% Li salt solution [32]. Recently, Vidal et al. [94] estimated the safe level of Li for aquatic life to be 2.5 mg L^{-1}; above this concentration, American bullfrog tadpoles (*R. catesbeiana*) showed upregulation of thyroid glands and reduction of normal activity. As shown above, Li impacts aquatic life in various ways. Estimating Li levels in different fish organs would help determine the daily intake of Li through this important food source for many people. Preliminary studies on Li toxicity levels have focused mainly on its effects during embryonic development and in plasma membrane proteins in early embryos. However, further functional studies are required, particularly concerning high Li production and consumption.

8. Li exposure in humans

Li was first approved as a mood-stabilizing drug for the treatment of manic disorders by the United States Food and Drug Administration [95]. It represents one of the most effective psychopharmacological agents for treating bipolar disorder and remains the first-line treatment in Canadian guidelines [96]. The

American Psychiatric Association and British Association of Psychopharmacology recommend starting doses of 300 and 400 mg day^{-1}, respectively, with maintenance doses varying from patient to patient, but aiming at a safe plasma concentration of 0.6–0.8 mM L^{-1} and compulsory monitoring every 3–6 months. The Royal Australian and New Zealand College of Psychiatrists recommends a starting dose of 500–750 mg day^{-1} and a single dose to achieve a plasma concentration of 0.6–0.8 mM L^{-1}, although the safe serum level is set to 0.8–1.2 mM L^{-1} [97]. The prescribed oral therapeutic dose of Li is usually within 600–1200 mg Li_2CO_3 day^{-1} (equivalent to 113–126 mg Li day^{-1}) [98]. Elevated levels of Li in living organisms facilitate its consumption by humans. Furthermore, previously recommended Li intake levels are outdated and demand reconsideration.

8.1. Li intake through the food web

Li is emerging as an important trace element in human nutrition, to whom it is available through the food chain [113]. The amount of Li in the human body is approximately 7 mg [14], with a recommended daily allowance of 1 mg [114,115]. Li intake through ingestion depends on its concentration in food and varies based on soil Li levels. Li intake through food was calculated in different countries and is estimated at 348–1560 μg day^{-1}, which reflects its uneven distribution in the Earth crust. The average daily intake of Li for an adult (70 kg) ranges from 0.65 to 3.1 mg day^{-1} [20] and is usually met through the consumption of food and drinking water. The previous study reported the Li concentration (4.6 mg kg^{-1}) in spinach grown in Jordan valley (water-soluble Li 0.95–2.68 mg L^{-1}), as well as documented that the consumption of 250–300 g fresh weight of spinach day^{-1} (estimated daily intake 1.15–1.38 mg day^{-1}) fulfilled the recommended daily intake of Li (1.0 mg day^{-1} for 70 kg adult). Furthermore, the estimated daily intake of Li through lettuce (0.09 mg day^{-1}), cabbage (0.12–0.48 mg day^{-1}), and green onion (0.18 mg day^{-1}) is less than recommended daily intake [13]. Figueroa et al. analyzed the Li concentrations in tomato (6.9–12 ppm), corn (1.0–13.48 ppm), and garlic (8.25–19.29 ppm) samples which were taken from the north of Chile [116]. Caballero et al. [117] suggested that bakery items (bread, pastries, and cakes) were a poor source of Li; all vegetables and potatoes contained >1.0 mg kg^{-1} Li, while lemons and apples contained about 1.4 mg kg^{-1}. Spices have a fairly high amount of Li, but their minute dosage in food does not contribute much to the dietary intake of Li. Mustard is rich in Li (3.4 mg kg^{-1}), whereas eggs, liver, and kidneys of cattle are even richer (5 mg kg^{-1}). Primary dietary sources of Li intake for humans include vegetables and grains (0.5–3.4 mg kg^{-1}), dairy products (0.5 mg kg^{-1}), and meat (0.012 mg kg^{-1}) [118]. Given that the aforementioned studies have some flaws regarding testing methodology, and Li concentration in the soil (Table S1) and food sources (Fig. 5) has increased substantially over time, it is highly recommended to reconsider Li intake through the food web and draw proper threshold levels of Li at country and district levels.

Keeping in mind, the importance of Li in metabolism and other body functions, including therapy for bipolar disorder, the USA, Japan, Germany, Denmark, and Mexico have already estimated the daily intake of Li. Countries with extensive Li mining activities, such as Australia, must reassess the daily Li intake. China, another large consumer of Li, is similarly deficient in estimating the daily intake of Li from foodstuffs. In the second step, the occurrence of Li in the diet and its daily intake could be correlated with crime and suicide rates or maniac disorders. Furthermore, there is a research gap regarding the magnification of Li in cereals, pulses, and other daily consumable plants and vegetables. So far, no studies have been reported to evaluate the trophic transfer (TTF) and biomagnification of Li from food to other living organisms. Detail investigations are needed to elucidate the risk of TTF to the food web and potentially to human health.

8.2. Consequences of Li exposure on human health

Low levels of Li are associated with higher rates of depression and anxiety, insomnia, sensitivity to stress, chronic pain, and a decline in natural healing processes, memory, and learning ability [16]. Li salts, such as Li_2CO_3 and $LiCH_3COO$, are used to treat manic-depressive disorders; however, off-label therapeutic use of Li_2CO_3 is toxic to the muscular, cardiovascular, gastrointestinal, urinary, and nervous systems in humans, having the potential to cause death [119]. Short-term exposure to Li (months to years) causes nephrogenic diabetes insipidus, polyuria, polydipsia, dehydration, a defect in urinary concentration, and thirst. Chronic higher Li dose therapy may increase the chances (6–8 fold) of developing the end-stage renal disease [120]. Moreover, drugs reducing the glomerular filtration rate might inflict chronic toxicity [121]. The lower/higher levels of Li in humans reflect etiological factors for different conditions. Studies should focus on the above diseases and Li deficiency issues to understand the underlying mechanisms.

Li intake beyond the therapeutic level (200–400 mg kg^{-1}) leads to Li toxicity due to impaired excretion and affects all vital organs [122] (Fig. 5). The half-life of Li is 12–27 h, but may reach 48 h in patients suffering from chronic Li intoxication [123]. Li clearance from the kidneys occurs at a rate of 10–40 mL min^{-1}, although it may increase to 58 h in elderly patients [6]. Li ingested through dietary intake or treatment tends to accumulate in the liver, bone, muscle, thyroid, brain, and kidneys (Fig. 5). The thyroid and kidneys accumulate the highest amounts of Li [124]. Like other water-soluble drugs, Li is also directly removed from circulation in the urine and bile. In patients suffering from liver disease, maintaining adequate blood serum levels of Li is challenging owing to changes in body fluid status [125]. Signs of Li toxicity depend primarily on the system involved; however, signs related to the renal and nervous systems are most common.

Endogenous Li blood plasma levels range around 0.4–1.2 mM L^{-1} [126], which is close to the toxicity limit (>1.5 mM L^{-1}) [127]. Although the therapeutic index for Li is very narrow and signs of toxicity, such as tremors and vomiting, become evident at concentrations of 1.5 μM L^{-1} [128,129], such physiological range of Li is still three times lower than the dose administered for therapeutic/prophylactic treatment of the bipolar disorder, whereby the concentration of Li in serum reaches 1.0 mM L^{-1} [130]. Renal toxicity due to Li is manifested through renal tubular acidosis, chronic tubulointerstitial nephritis, nephrotic syndrome, nephrogenic diabetes insipidus, and sodium-losing nephritis [131] (Fig. 5). Neurological effects include coarse tremor, hyperreflexia, nystagmus, and ataxia, with varying levels of consciousness and reversibility of signs [132]. When Li affects the central nervous system, patients experience lethargy, seizures, confusion ranging from mild to delirium, and even coma, in what is known as cerebellar dysfunction [133]. These neurological dysfunctions may last 12 months post-treatment and persist forever [132]. Elevated Li concentrations affect the musculoskeletal system, and manifest as coarse tremors and muscle twitching [134]. Li therapy affects the endocrine system and may cause myxedema coma, hypothyroidism, and goiter [135].

Li affects the cardiovascular system, whereby it changes the shape of the electrocardiogram in the T form wave inversion and creates conduction disturbances [136] (Fig. 5). Despite early inconclusive evidence [137], Li has since been proven to be teratogenic during the first trimester of pregnancy [138]. A recent study revealed that pregnant women undergoing Li treatment for bipolar

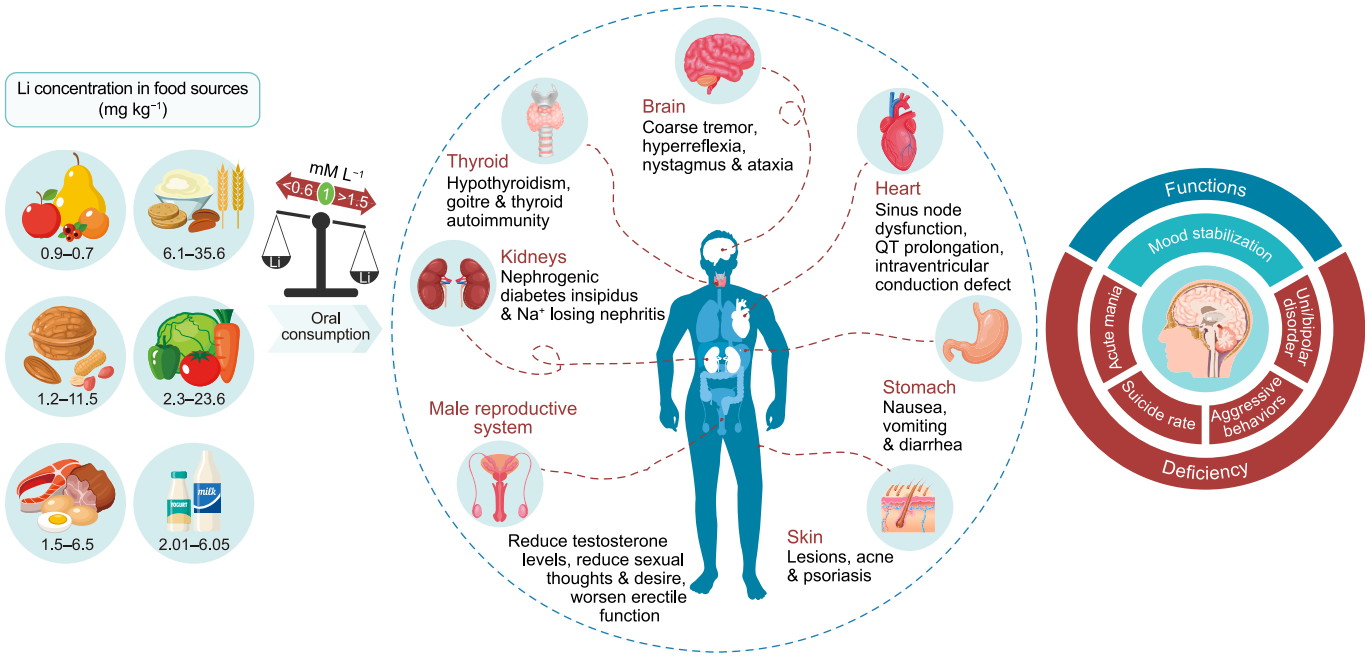

Fig. 5. Systematic framework depicting the interplay between Li and human health. The scheme starts with daily intake of Li and includes oral consumption balance and Li functionalities, as well as consequences for the human body.

disorder during pregnancy had higher chances of miscarriage (20.8%) compared to untreated women suffering a miscarriage (10.9%) [139]. Studies taking into account gender should be performed. One interesting option is fortifying foods via genetically modified plants, as this approach does not alter food quality. Moreover, the World Health Organization and other health governing bodies should identify common safe and toxic limits of Li in the serum, together with daily intake recommendations. Finally, the concentration of Li in foods should be monitored, especially in geographical areas with active Li mining.

9. Key determinants of Li abundance in the living environment

Key drivers determining the presence of Li in the environment include soil, plants, animals, and humans (Fig. 6).

(1) The growing reliance on a digital economy has dramatically increased the use of Li-ion batteries, posing a long-term threat to soil ecology and crops. No detailed investigation regarding the impact of Li on soil organisms has been reported, calling for a global framework on the adverse effects of Li in soil ecosystems.
(2) The elevated mobility of Li leads to its accumulation in plant leaves, which endangers the food web. Plant scientists should conduct studies regarding the trophic transfer of Li along the terrestrial food chain and its effect on end consumers.
(3) Recently, *A. venetum* and *Apocynum pictum* have been identified as capable of storing large amounts of Li in their leaves without developing toxic symptoms. Genes responsible for Li accumulation in these plants could be transferred to food crops, such as beans, cereals, and leafy vegetables, to be planted in Li-contaminated soils. Such practice would provide a double benefit, allowing soil reclamation while also supplying crops rich in Li to potential consumers deficient in this micronutrient. Finally, to take full advantage of Li in the environment, future studies must ensure that the large data sets produced are fully exploited to better understand Li toxicity and tailor Li daily intake/deficiency.
(4) Domestic animals are major food sources for humans. An improved understanding of the mechanism and safety limits of dietary intake will help overcome Li deficiency-derived complications in living organisms.

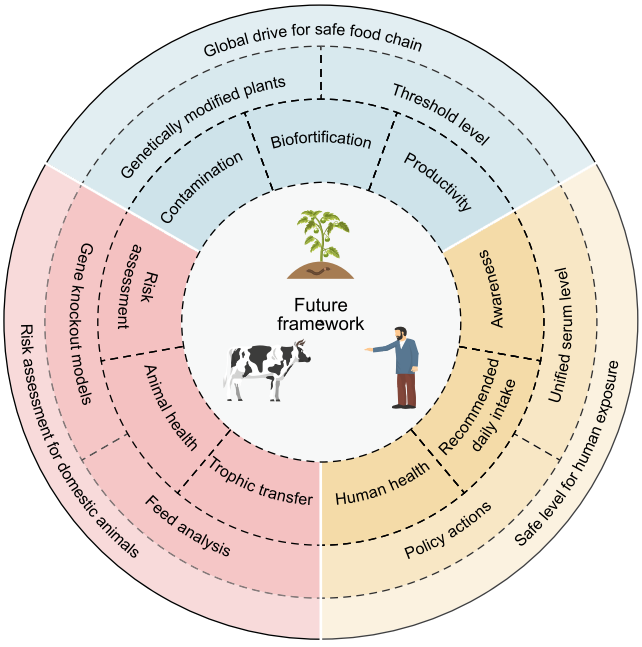

Fig. 6. Li exposure challenges and plans to ensure a safe and sustainable uptake of Li by plants, animals, and humans.

(5) The sustainable development of the technology sector should focus on an interdisciplinary approach that prevents excess Li release in the environment.
(6) Lithium plays an important role in mood stabilization, and a safe dosage must be established. To date, most conclusions have been drawn based on experiments in rats, whose implications are difficult to extrapolate.

10. Conclusions and future perspectives

The present review provides an overview of Li distribution and its accumulation in the environment. We have critically evaluated Li daily intake, bioaccessibility, mechanistic approaches, and possible risks associated with Li exposure by all environmental compartments (see figures). The present study offers an important and unifying perspective for life scientists and environmental researchers regarding the growing role of Li in our ecosystems and society. Elevated Li levels exert a toxic effect on plant physiology and biochemical activity. Li interferes with the translocation of other essential elements, such as Mg, Ca, and K. Li accumulates preferentially in the aerial portion of terrestrial plants but has been shown to have an effect also on aquatic life (e.g., fish, amphibians, and invertebrates), with numerous studies focusing on Li levels in different organs. A high concentration (0.45 M L^{-1}) of Li causes a significant release of domoic acid in aquatic species, affects embryonic development, and causes microcephaly. Li enters the food chain through plants and drinking water, with its daily intake in humans ranging from 0.65 to 3.1 mg. The safe level of Li in blood plasma is 0.6–1.2 mM L^{-1}, with signs of toxicity appearing $\geq$1.5 mM L^{-1} and life-threatening conditions apparent $\geq$2.0 mM L^{-1}. Li has therapeutic efficacy in treating bipolar disorder and other manic conditions. Low levels of Li (<0.6 mM L^{-1}) in blood plasma are associated with depression, insomnia, sensitivity to stress, and chronic pain. Toxic systemic effects of Li (>1.5 mM L^{-1}) manifest through renal toxicity, neurological symptoms, coarse tremors, and muscle twitching. Given the above evidence, the following points require further research.

(1) Extensive data on Li concentration in the natural environment across countries will inform on a safe environment and sustainable development.
(2) Specific studies are needed to evaluate the interplay between Li and heavy metals, such as lead, copper, and cadmium, in the soil and how co-exposure to these metals determines Li availability in the rhizosphere.
(3) Studies need to be planned to unveil the changes in the nutritional composition of plants, especially in vegetables and Li-accumulating *Brassica* spp. along with leguminous bean crops. At the same time, the underlying mechanism of Li-induced toxicity in plants needs to be explored.
(4) Areas with ongoing mining activity lack studies on Li daily intake and the diseases caused by Li toxicity or deficiency in those areas.
(5) Due to higher mobility, Li can easily be accumulated in plants which demands additional investigation regarding the TTF of Li to higher levels of the food chain.
(6) Importantly, regulatory thresholds listed by the World Health Organization are outdated and need a thorough update as the concentration of Li in the environment continuously increases and poses a serious risk to human health.

CRediT authorship contribution statement

Noman Shakoor and **Muhammad Adeel:** Writing - original draft, Conceptualization, Visualization. **Muhammad Arslan Ahmad:** Writing - review & editing, Conceptualization. Muhammad Zain, **Usman Waheed**, **Rana Arsalan Javaid**, **Fasih Ullah Haider**, **Imran Azeem**, Pingfan Zhou, **Yuanbo Li**, **Ghulam jilani**, and **Ming Xu:** Writing - review & editing. **Jörg Rinklebe** and **Yukui Rui:** Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this work.

Acknowledgments

This research was funded by the The 111 project of the Education Ministry of China (B18053), The National Natural Science Foundation (32130081). The authors truly thank Xiaoli Song from JOYO Technology Co. LTD for helping with figure preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ese.2023.100252.

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