

## **Part I: The Biological System of the Chemical Elements (BSCE) and the role of Lithium for mental health care**

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### **ABSTRACT:**

In order to account for the physiological effects of chemical elements in living organisms using some Biological System of Elements (BSE) established by Markert in 1994 [1], the familiar Periodic Chemical System of Elements (PSE) according to Mendelejew and Meyer from 1869 was completed and modified using the Geochemical System of Elements (GSE) by Railsback [2-4, 5]. BSE goes beyond accumulating essentiality investigations, despite obvious technical and analytical limitations. In correlation among abundances of elements in different samples of biological origins, there are deep-rooted biochemical factors and relationships which these authors began studying and describing in more detail in the late 1990's. Until the end of 2017, the BSCE was referred to as the Biological System of Elements (BSE).

Lithium is not considered a vital or essential trace element. However, Li is present in our body and has important functions, especially for the psyche. Specifically, Li is important for mental health. The application of Li as pharmaceutical therapeutic equivalent for bipolar

disorders (formerly called manic depressive disorders) is a well-known example of the use of a monovalent cation on neurological therapy. One of the main scientific objectives of this review and future research is the use of functional food in supporting and balancing the therapeutic dose of Li in the human body. In order to describe a possible application of a "functional food therapy by Li" and to meet its "scientific philosophy" a first look was given to Li-accumulating plants. We explain the use of plants containing high amounts of Li and described possible effects of increased Li concentrations in the human body.

Finally, we should confirm if "natural food therapy" (for instance "green pills") can positively support mental human health care benefits by fitting the ratio of Li / neurological diseases. For example, diseases like chronic bipolar disorders. Accordingly, the BSCE will continue to identify and investigate other chemical elements for using them in an effective Functional Food Therapy (FFT) of chronic neurological diseases and possibly other diseases. **Keywords:** Biological System of Chemical Elements (BSCE), Lithium (Li), Bipolar Disorders, Neurology, Functional Food Therapy (FFT), Chronic diseases

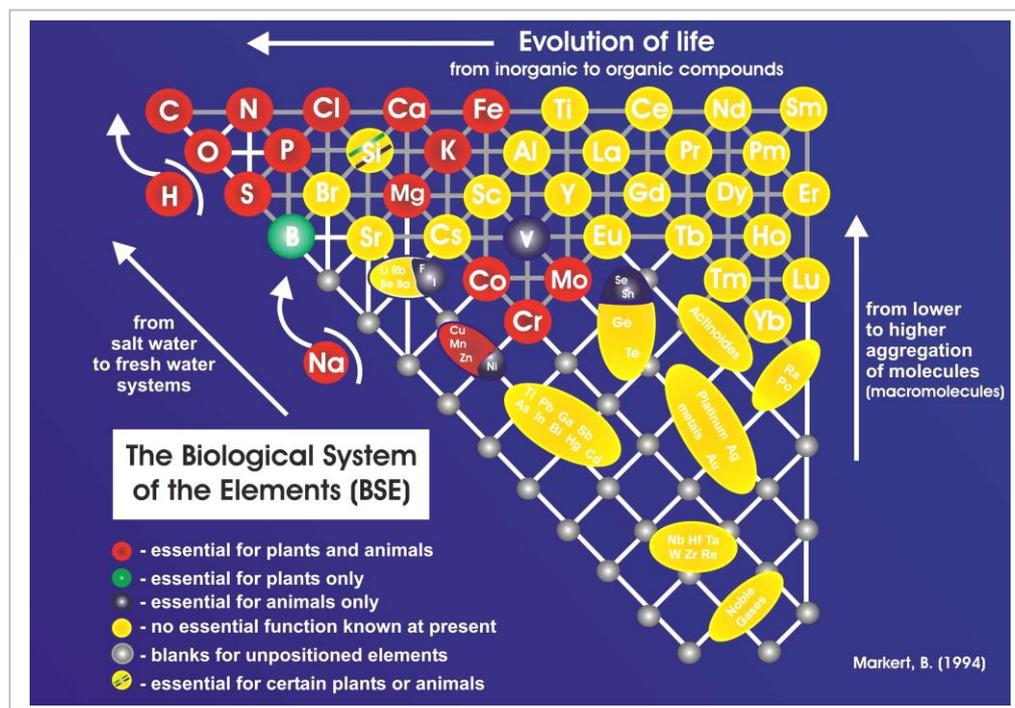
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## **AN INTRODUCTION INTO THE BIOLOGICAL SYSTEM OF THE CHEMICAL ELEMENTS (BSCE)**

The position and classification of the chemical elements in the Periodic System of the Elements (PSE) according to Mendelejew and Meyer (1869) does not allow any statement to be made about their functional essentiality or their acute or chronic toxicity for living organisms. The PSE is based on purely physiochemical aspects [6].

Mendelejew wrote about the Periodic Table in the first volume of the Journal of the Russian Chemical Society in 1869. While working independently, Dimitrij Mendelejew and Lothar Meyer developed the basis for the present periodic table. Mendelejew published his work as "The dependency the chemical properties of the elements of atomic weight." In the process, 63 elements were grouped in ascending order according to the atomic mass in seven groups with similar properties. The same principle was also established through Meyer. However, Mendelejew could have better represented his work by following his system predictions about missing elements and their properties. His system found worldwide recognition [2-4].

Therefore, the attempt has been made to develop a Biological System of Elements (BSE), with preliminary consideration of the aspects of basic biochemical and physiological research. Due to the inadequate chemical description of biological and medical relationships in the Periodical System, the Biological System of the Elements (BSE) was first established in 1994 (Figure 1). Since 2018, the BSE or the Biological System of the Elements has been referred to as the Biological System of the Chemical Elements (BSCE). The main factors for establishing this first "intuitive" system have been accurate and precise multielement data including representative sampling procedures, interelement relationships, physiological function of elements, uptake mechanisms, and evolutionary aspects [1].



**Figure 1:** The Biological System of Elements (BSE) for terrestrial plants (glycophytes) [1]. Since 2018, the BSE or the Biological System of the Elements (BSE) has been referred to as the Biological System of Chemical Elements (BSCE).

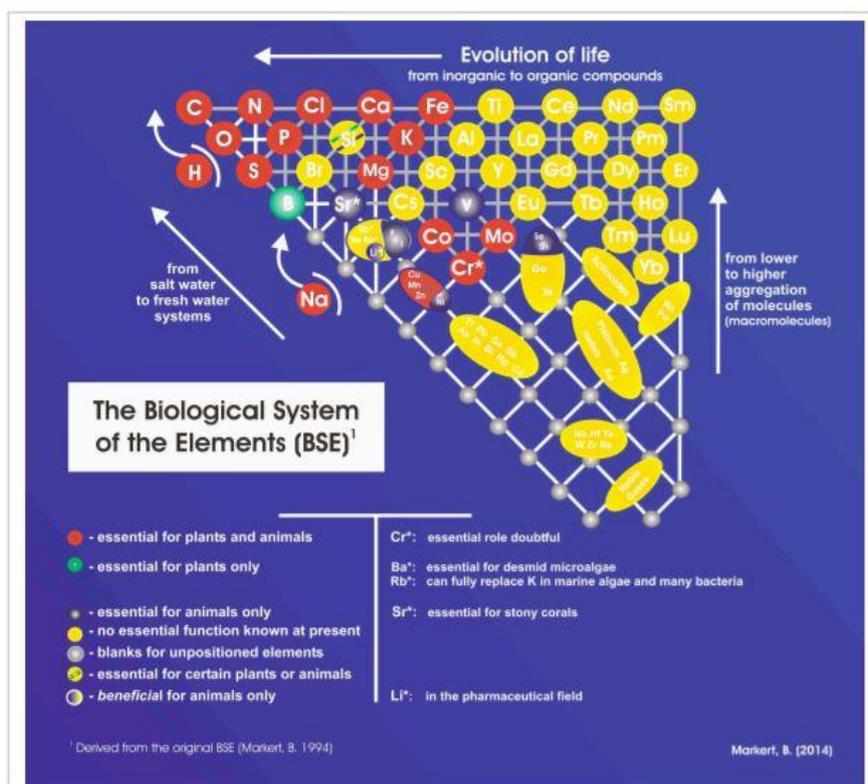
The diagram shows relationships among the elements together with their corresponding essential functions (colours), extent of biochemical functions, and the corresponding capacity to form macromolecules by condensation reactions (vertical arrow at right side of diagram). While in “pure” geochemistry oxophilic metals produce the most complicated condensation products (i.e. clay minerals) there was a shift towards non-metal based structures during chemical and biological evolution which afforded polymeric structures based on the latter (C, N, O) (horizontal arrow to the left). The diagonal arrow refers to changes of concentration from ocean to freshwater. There is a substantial decrease of concentrations in some elements (Mg, Sr, Cl, Br) from ocean to freshwater, requiring them to be enriched by biomasses if their biochemical use is to be continued. These kinds of enrichment can only be accomplished by means of certain biochemical features which involve properties and/or components of the corresponding biogenic materials, many of which are specific for at least one species in their particular combination [1, 6].

The complication within the system of these elements is based particularly from data on the multielement analysis of terrestrial plants. We compiled data from standard reference materials from the National Institute of Standards and Technology (NIST, Gaithersburg, U.S.) and highly accurate research samples. The data pool for plant reference materials is composed of certified element contents for citrus leaves (NIST SRM 1572), tomato leaves (NIST SRM 1573), pine needles (NIST SRM 1575), and Bowen’s kale [7]. The data pool was supplemented by multielement data spectra from the following plants: leaves of *Betula pendula*, needles of *Pinus sylvestris*, leaves of *Vaccinium vitis-idaea*, leaves of *Vaccinium myrtillus*, the aboveground parts of *Deschampsia flexuosa*, *Molinia caerulea*, *Polytrichum formosum*, and different *Sphagnum* species. All the plants were gathered during the 1987

vegetation period on Grasmoor near Osnabrück [8] We used only data from terrestrial plants of freshwater systems (glycophytes). The results of typical accumulator plants or halophytes did not enter the database, with the exception of data from Polytrichum and Sphagnum species [7, 9-18].

As the BSE was first conceived in 1994, BSE diagrams have been translated into many languages including Chinese (Mandarin), French, German, Latvian, Lithuanian, Persian (Farsi), Polish, Spanish due to the support and discussion from many colleagues around the world. Arabic, Italian, Hindi, Russian, and other translations are being developed [19-25]. All translations can be found at [www.eisn-institute.de](http://www.eisn-institute.de).

Meanwhile, further research has shown there are exceptions to the role of certain elements to specific bacteria, plants, animals, and humans [6]. Therefore, the original BSE was extended into a modified BSE (Figure 2) where Cr, Ba, Rb, Sr, and Li will likely take the following role (more detailed information on the functionality of each chemical element can be read in Markert et al. 2015 [6]): The essential role of Cr is doubtful for plants and animals; Ba is essential for desmid microalgae; Rb can fully replace K in marine algae and many bacteria; Sr is essential for stony corals; Li has a beneficial effect to animals (humans) in the pharmaceutical field.



**Figure 2:** Extended Biological System of the Chemical Elements after Markert (1994) [1] showing exceptions of the role of certain elements to specific bacteria, plants, animals and human [6]. Since 2018, the BSE or the Biological System of the Elements (BSE) has been referred to as the Biological System of Chemical Elements (BSCE).

### BENEFICIAL ROLE AND FUNCTION OF LITHIUM FOR MENTAL HEALTH CARE

Li is a silver-white, soft alkali metal and the lightest of all metals. Lithium was discovered in rocks in 1817. Lithium is called Lithos in Greek. A specific distribution pattern of Li in the

environment is given in Part 2 of this publication series [26]. This metal is used in rubber production, the manufacturing of batteries, X-ray films, and for alloys with copper, lead, and nickel.

As a trace element, Li has been generally regarded as non-essential for humans. However, multiple therapeutic effects, especially on the psyche, using this metal have been demonstrated [27-44]. After studies by Ekmekcioglu [45] and Quiroz et al. [46, 47], there has been no exactly known physiological function of Li in any living being. Accordingly, Li cannot be taken as an essential element. Regardless, lithium supply will still have a beneficial effect in certain circumstances. According to Anke [48], Li depletion—induced in either rats or goats by corresponding food composition—will bring about problems concerning both metabolism and reproduction, which suggests there are conditions in which Li may also be important to humans. In particular, Li is well-known to be beneficial in bipolar depression (see below), which suggests lithium may be regularly involved in neurophysiology or CNS (Central Nervous System) brain function. In both whole-animal and tissue experiments, pharmacological doses of Li were shown to be active in biochemistry.

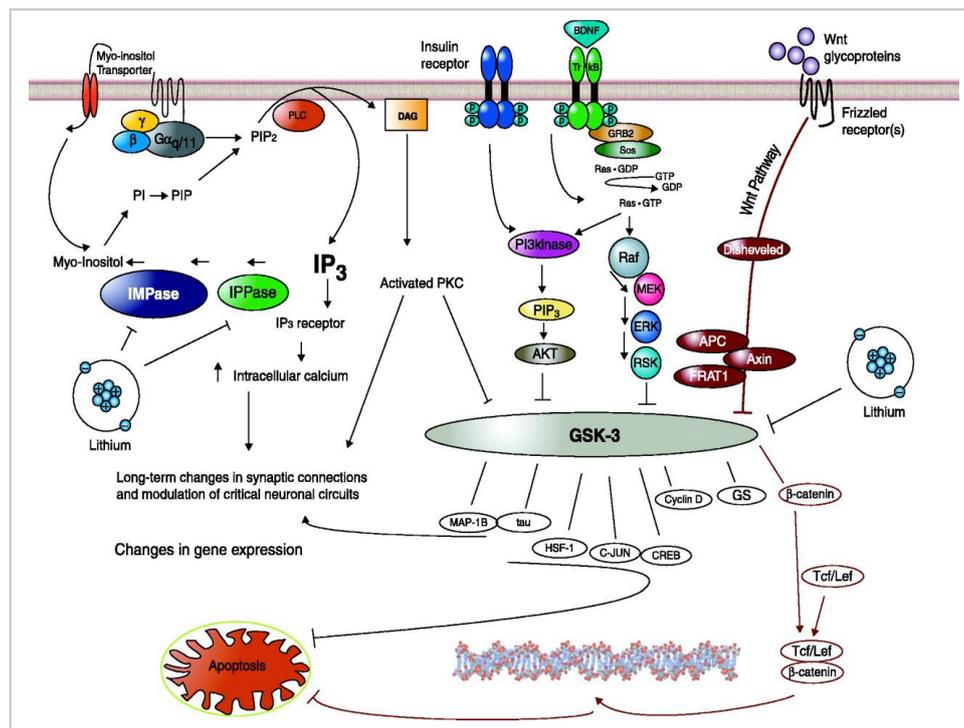
We have listed some of the effects of Li and Li compounds in animals and various cell lineages after Ekmekcioglu [45]: Stimulation of hematopoiesis; altering activity of secondary messengers (adenyl cyclase ↓, phospholipase ↑); effect on inositol metabolism; effect on prostaglandin metabolism; suppression of Na<sup>+</sup> /K<sup>+</sup> -ATPase; change of circadian rhythms; effect on neurotransmitter metabolism. We must acknowledge Li administration is highly dangerous if combined with antipsychotic drugs like haloperidol or fluphenazine, causing toxic encephalopathy and sometimes irreversible brain damage. In this case, compounds interact with the dopamin rather than the serotonin system; antibacterial and antiviral activities; effects on ion and water transport channels (due to extreme hydration, in addition to displaying some lipophilicity. Li<sup>+</sup> is even much bigger in aqueous media than either Na or Cs cations); neuroprotective effects; suppression of some enzymes involved metabolism, like phosphoglucomutase in glycogenolysis.

Studies have not confirmed whether these effects also apply to humans already exposed to levels of Li, which are common in and from nutrition [45].

In 1949, Cade was the first to report positive effects on manic illness. This prompted numerous researchers to investigate the activity of Li in bipolar affective disorders (then called maniac depression). These researchers demonstrated how Li administration would inhibit further maniac or depressive episodes among the majority of patients. This made Li salts the medication of choice in treating bipolar affective disorders for quite a period of time already [49]. However, more recent reports and studies have demonstrated Li therapy to be more efficient in precluding maniac recursions than for treating depressive components/phases. Until now, the way Li works in bipolar disorders has not been completely clear. Regardless, Li does influence the activity of secondary messengers. According to Quiroz et al. [46, 47] the effect of Li on inositol metabolism seems to be pertinent (Figure 3).

Inositol phospholipids are involved in various processes of information processing in the brain [50] (e.g. being important for receptor-mediated signal transduction). After G proteins and phospholipase C had been activated, 1,4,5-inositol triphosphate and diacylglycerols form and initiate different kinds of intracellular reactions. These include Ca<sup>2+</sup> ion release and regulation of ion channels in addition to enzymes. An increased activity of this signal

transduction system is likely to produce increased intra-CNS release of neurotransmitters like serotonin or dopamine.



**Figure 3:** Glycogen synthase kinase-3 (GSK-3) and inositol monophosphatase (IMPase) are direct targets of lithium.

The figure highlights relevant interactions among intracellular pathways related to lithium’s action. GSK-3 functions as an intermediary in a number of signaling pathways including neurotrophic signaling pathways, the insulin–phosphatidylinositol 3 kinase (PI3K) pathway, and the Wnt pathway. The activation of these pathways inhibits GSK-3. The upper left portion of the figure depicts lithium’s actions on the PI signaling pathway. Activation of some G proteins induces phospholipase C hydrolysis of phosphoinositide-4,5-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol-1,4,5-triphosphate (IP3). DAG activates protein kinase C (PKC). IP3 binds to the IP3 receptor while also functioning as a calcium channel in the cell. IP3 is recycled back to PIP2 by IMPase and inositol polyphosphatase phosphatase (IPPase), both of which are inhibited by Li [51]. The inositol depletion hypothesis suggests that Li exerts its therapeutic actions by depleting free inositol, which thereby dampens the activation of downstream signaling pathways in neurons [34]. The figure and text were reproduced with permission from H. Manji (one of the authors of Gould et al. 2004) [52].

Li has a variety of effects on the central nervous system. Studies have not yet fully clarified which specific effect is ultimately responsible for effectiveness, especially in the case of bipolar disease. The effectiveness may be the result of various different effects. Li is not only effective in bipolarity but also for many other diseases which are likely to be caused by mental or central nervous mechanisms [74]:

1. Inactivation of ion channels: Li acts similarly to anticonvulsants (medicines against epilepsy) in the cellular Na K stream and may reduce the central excitability of the brain.

2. Effect on second-messenger-systems: All functions of life take place at the smallest cell level. Among the main executive instruments are enzymes and proteins. By interfering with such enzyme chains (Fig. 3: Inositol monophosphatase inhibition), Li leads to a reduction of certain enzyme products and their secondary products (Fig. 3: Inositolphosphatidylinositol). The inhibition of these (and other) products leads to a decrease in the Ca concentration in the cells. And this is exactly what is required in the case of bipolar disease, since intracellular Ca concentration is typically increased in the case of bipolar disease.
3. Release of GABA: GABA (gamma-Aminobutyric acid) is a messenger substance in the brain which is directly linked to mood, like other messengers. Li increases the release of GABA
4. . Serotonin increase: Li leads to an increased release of the "mood transmitter" serotonin and simultaneously inhibits its degradation.

Major depressive disorder (MDD) affects millions of patients [27, 32]. However, the pathophysiology is not well understood. Rodent models have been developed using chronic mild stress or unavoidable punishment (learned helplessness) to induce features of depression such as general inactivity and anhedonia [27, 32]. Ries et al. [32] recently reported a threeday vibration-stress protocol for *Drosophila* which reduces voluntary behavioural activity. As in many MDD patients, lithium-chloride treatment can suppress this depression-like state in flies. The behavioral changes correlate with reduced serotonin (5-HT) release at the mushroom body (MB) and can be relieved by feeding the antidepressant 5-hydroxy-L-tryptophan or sucrose, which results in elevated 5-HT levels in the brain. This relief is mediated by 5-HT-1A receptors in the  $\alpha$ - $\beta$ -lobes of the MB, while 5-HT-1B receptors in the  $\gamma$ -lobes control behavioral inactivity. The central role of serotonin in modulating stress responses in flies and mammals indicates evolutionary conserved pathways can provide targets for treatment and strategies to induce resilience [32].

Highly impressive findings have discovered Li must have a positive influence in reducing the suicide rates [28-31]. In Japan, the suicide rate is particularly high. About 30,000 Japanese people have ended their lives every year since 1998. According to the WHO, in 2006 there were 29,921 people who no longer wanted to live, two-thirds of whom were men: about 100 people a day took their lives. Based on these statistics, the rate is 23.7 per 100,000 people (male: 34.8). In 2007, more than 33,000 people lost their lives. In 2008 there was a slight decrease back to 32,249. However, in January 2009 2,645 people killed themselves, which is 15 percent higher compared to that of January 2008. One possible factor was the recession. In Japan, this is called a suicide epidemic [60, 61]. Lithuania still beats Japan with 38.6 suicides per 100,000 inhabitants. The suicide rate in Russia is also very high (32.2). In Germany, which occupies a medium position, 13 out of 100,000 people die, and the trend is falling. But in Germany there are far more men than women who take their lives. However, in Germany the majority of people who commit suicide are over 65. People 75 years and older in Germany, 45-54 year-olds and those over 75 years of age in Russia, and 55-64 year-olds in Japan are the most at risk (i. e. when working life ends and retirement begins or is in prospect) [60, 61].

As reported in the British Journal of Psychiatry, Japanese psychologists and psychiatrists from the universities of Oita and Hiroshima have discovered that even small amounts of Li can reduce the propensity to suicide [60]. For their study, they examined the drinking water of the 18 communities of the prefecture of Oita on the island of Kyushu for the naturally

occurring Li concentrations. The different values, which varied considerably and ranged from 0.7 to 59 micrograms per liter, was compared with suicide rates in the communities. The result between the years 2002 to 2006 was the following: the communities with the highest Li levels in drinking water had the lowest suicide rates. Even if the concentration was very low, scientists suspect that the constant intake could have a cumulative effect [59, 60].

Kapusta et al. [30] confirmed for Austria that there is a negative correlation between suicide incidence levels and Li concentrations in drinking waters which had been noticed before on other continents. Yet there are no viable conclusions concerning a causal relationship between the values. Accordingly, there are no implications for conducting suicide prevention by adding low amounts of Li to food or water.

According to Sugawara et al. [61], Li has been used as a mood-stabilizing drug in people with mood disorders. Previous studies have shown that natural levels of Li in drinking water may protect against suicide. The study conducted by Sugawara et al. [61] evaluated the association between Li levels in tap water and the suicide standardized mortality ratio (SMR) in 40 municipalities of Aomori prefecture, which has the highest levels of suicide mortality rate in Japan. Li levels in the tap water supplies of each municipality were measured using inductively coupled plasma-mass spectrometry. After adjusting for confounders, a statistical trend toward significance was found for the relationship between Li levels and average SMR among females [61]. These findings indicate that natural levels of Li in drinking water might have a protective effect on the risk of suicide among females [61]. Future research is warranted to confirm this association.

Typical groups for a surplus of Li: In chronic bipolar and partly in unipolar depression [62]; in the case of mental instability, especially in the case of aggressive behavior; in gout and uric acid stones; for the purpose of immunostimulation, especially with the accompanying treatment of cancer diseases; in alcoholism; possibly also for external use in herpes, fungi, and eczema (Li-containing ointments and water).

Li preparations contain a much higher dose of Li than one could ever consume over the normal diet: concentrations of about 200 milligrams (mg) of Li per day are common in a therapy. In contrast, on average only 0.8 mg of Li per day is observed.

The use of Li as a medicament is only recommended under medical supervision. In clinical psychiatry, Li is used primarily for the treatment of affective disorders, as well as for headache attacks in the context of migraine or cluster headaches. The side effects of Li therapy, as with all drug treatments, are primarily dependent on the specific sensitivity of the patient to Li. Pure Li gifts - not the often used combination gift with other psychopharmaceuticals - are relatively rare. Only very occasionally massive symptoms of poisoning occur [6, 63-67]. If the patient is well adjusted and observed during therapy, signs of side effects can usually be detected at an early stage. The side effects usually depend on the dose. Common side effects are for example [74]: increase in weight; frequent urination; thirst; nausea, diarrhea, vomiting.

In the area of neurological side effects (nerve and muscle function) the following phenomena can occur in relatively rare cases when taking Li [74]: muscle weakness; muscle tremor; movement disorders; reduced nerve conduction velocity; interference with reflexes; Nystagmus; visual field failure; disturbances of memory and concentration.

## LITHIUM USE IN PRACTICE

"I don't believe in God, but I believe in lithium" is the title of an article from the New York Times magazine in 2015 where American journalist Jaime Lowe described her twenty years of struggle with bipolar suffering [68-71]. She revealed what happened when she tried to cope without the medicine. After seven years of therapy, Lowe stopped using the drug at the

age of 24. Afterwards, Lowe wore hundreds of necklaces at once, spent a fortune on butternut pumpkin, growled and yelled instead of talking, and wanted to challenge President George Bush to a speech duel [68].

The potential of Li not only to protect against mania but also possibly against dementia has also been demonstrated in animal experiments [68]. If rats were mixed with trace elements in food, their memory increased. Bipolar patients also seemed to benefit; with Li therapy, the memory functioned in the long term better than without. In 2011, Brazilian physicians tested the drug with 45 seniors with first slight memory weaknesses and were actually able to slow down mental decline. High doses were not even necessary for these effects, which was demonstrated by colleagues with only one five hundredths of the crowd [68].

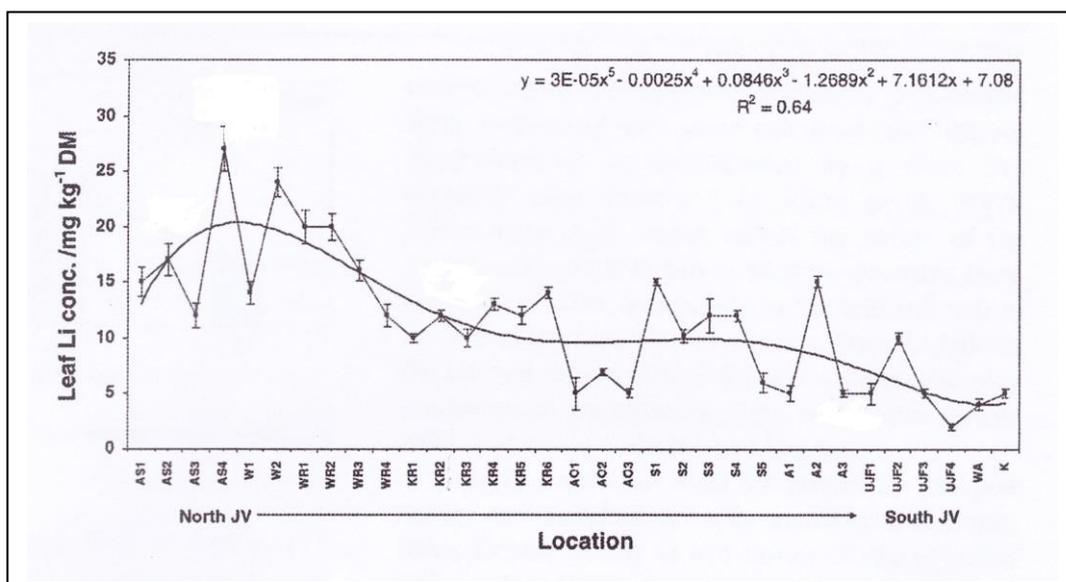
The result shocked Danish physician Lars Kessing at the psychiatric center of Copenhagen University [68]. The concentrations to which every human being is exposed in everyday life were obvious. Li is practically everywhere, within drinking water, milk, meat, eggs, and vegetables [68]. "And this day in and day out," says Kessing, who took care of the Danish population register in order to find a possible influence on the risk of dementia with very high Li concentrations in drinking water. People actually suffer less from Alzheimer's disease, as Kessing [72] reported in the JAMA Psychiatry trade journal in summer 2017 [72]. However, the risk of dementia did not increase correspondingly at low concentrations, as would be expected in a causal connection. While these remain unproven [72], Kessing believes "it is quite possible that the active ingredient could play a role in the prevention of dementia" [68].

## **OUTLOOK: MEETING FUNCTIONAL FOOD PHILOSOPHY**

To address the functional food philosophy (Danik Martirosyan) of using the intake of microbes, plants, or animals for health care benefits, the relationship of Li to neurological diseases will be discussed.

According to the high (positive) influence which is given by Li pharmaceutical intake to bipolar disorders and the effect the given by Li to lower suicide attempts found in Japan, Austria, and Texas, a suggestion was to use Li accumulating plants to balance Li distribution in human body. Suggested plants includes those from the plant family of Solanacea (i.e. tomato, potato, and paprika), which are are well known for accumulating Li under specific conditions.

For example, Ammari et al. [73] described the occurrence of Li in the environment of the Jordan Valley and its transfer into the food chain. The study was conducted to investigate the concentration and distribution of water soluble Li in solid of the Jordan Valley and its concentration in citrus trees and some important food crops in view of the significant implications of Li for human health. The concentration of soluble Li was measured in 180 soil sample collected at two depths (0-20 and 20-40 cm), while its content was determined in fully expanded leaves collected from citrus and different vegetable crops [73]. Concentrations of soluble Li in soils vary from 0.95 to 1.04 mg/l in topsoil and from 1.06 to 2.68 mg/l in subsoil, while Li concentration in leaves ranged from 2 to 27 mg/kg DM (Figure 4). Li concentration of the same family or different families vary with location in the valley (e.g. they decreased from north to south). Soluble Li in soils and the plant family did not solely affect Li transfer in the food chain. Furthermore, soil EC, Ca, Mg, and Cl, which increased from north to south might adversely affect plant Li uptake. The current study has demonstrated how consuming 200-300 g FW of spinach per day and per person is recommended to provide consumers with their daily Li requirement for significant health and societal benefits [73].



**Figure 4:** Leaf Li concentration of various common (food) crops grown in different locations of the Jordan Valley [73].

Scientific findings to date, some of which have been described above, suggest how Functional Food Therapy (FFT) using plants that accumulate high Li concentrations in the form of "green pills" should be discussed and potentially produced from plants which accumulate high levels of Li. In the second part of our lithium series, we will describe the distribution of the Li in different environmental compartments and present a model that allows us to describe the Li requirement for mental phase stabilization, which would also be combined with a positive mood stabilization [26]. It is important to keep the absorption of Li well below the toxicologically effective Li concentrations. The accumulated Li in foods such as French fries, potatoes, tomatoes, ketchup, paprika, gypsy sauce and more will move in areas containing only about 500 to 1000 times the concentration of Li, which would be toxicologically effective.

Further intensive scientific studies on Li metabolism, its genetic predetermination, and its biochemical and molecular-biological detectable dose effect curves in humans should be considered.

## ACKNOWLEDGMENTS

Many scientists have contributed to the development of the Biological System of Chemical Elements. Some of you have joined us on the "adventure" Li and its effect on the human psyche. They deserve our special thanks, as it has not always been easy to get involved in something quite new and a global developing field of work. This required courage from all of us to assert ourselves against some prevailing and pre-existing opinions. Finally, we would like to take this opportunity to thank the two independent reviewers who reviewed this article for their valuable advice on improving our manuscript.

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**Authors' Contributions:** All authors contributed to this review.

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