

## Review on the toxic effect of fluorine and lead on lichen metabolism

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**Abstract:** Thanks to their ability to absorb large amounts of trace elements from the atmosphere, lichens are widely used as bioaccumulators and bioindicators of air pollution. Among air pollutants, heavy metals represented by lead are the most important contributors to the deterioration of ecosystems. Fluorine is prevalent in a wide range of environmental matrices, even in trace amounts, and is one of the most phytotoxic halogens to plants. When lichens are exposed to air pollution, they frequently undergo structural, morphological and physiological alterations, and exhibit several coping strategies to combat and tolerate stressful situations. This manuscript presents general information about lichens, fluorine, and lead as well as the toxic effect of these two air pollutants on lichens, and the means of combat used by lichens to respond to fluorine and lead-induced stress.

## 1. INTRODUCTION

One of the major problems of current time is air pollution, the assessment of air quality through the use of lichens as bioindicators is a major concern at the moment. Lichens present a very important model of symbiotic organisms that include a fungus termed mycobiont, that captures fixed carbon from green algae and/or cyanobacteria called photobionts (Mitrović *et al.*, 2011; Calcott *et al.*, 2018). Because lichens have no roots and obtain their mineral nourishment from atmospheric inputs and moist deposits, they make good bioindicators of air pollution (Garty *et al.*, 2008; Gauslaa *et al.*, 2021). Lichens are also characterized by the presence of many original compounds, especially bioactive secondary metabolites (Mukemre *et al.*, 2021), which can be used for their antimicrobial (Maciąg *et al.*, 2014; Sargsyan *et al.*, 2021; Gandhi *et al.*, 2022) and antioxidant activity (Rodríguez *et al.*, 2016; Gessner *et al.*, 2017; Kandelinskaya *et al.*, 2021), the most important of which are polyphenols thanks to their pharmacological activity (Stromsnes *et al.*, 2021). Polyphenols have an important role in a plant's ability to withstand various stresses (Kiani *et al.*, 2021; Tuladhar *et al.*, 2021; Kołton *et al.*, 2022). They are necessary for plant's growth, nutrition, survival, and defenses (Singh *et al.*, 2021). Currently, lichens are being used for a variety of purposes, including the therapy of many human illnesses, especially as an anti-cancer activity (Nugraha *et al.*, 2019; Solárová *et al.*, 2020; Chae *et al.*, 2021; Šeklić *et al.*, 2022).

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Fluoride is one of the most phytotoxic chemical elements for plants and can be present in many different environmental matrices, even in small amounts (Banerjee & Roychoudhury, 2019). It affects the metabolic activity of plants by decreasing nutrient uptake, germination, photosynthesis, growth, and productivity (Sharma & Kaur, 2018). Fluoride toxicity causes the generation of reactive oxygen species (ROS), it has also a negative impact on enzyme activity, protein synthesis, and gene expression patterns (Choudhary *et al.*, 2019). Heavy metals inhibit chlorophyll production in lichens (Rola *et al.*, 2019). Abiotic stress has a major impact on photosynthesis in green plants at every stage (Ashraf & Harris, 2013). According to Nareshkumar *et al.* (2015), lead disrupts the prooxidant/antioxidant balance, resulting in a range of cell and tissue damage that eventually progresses to subcellular destruction.

When lichens are exposed to contaminants in the environment, they frequently undergo physiological, morphological, and structural alterations (Matos *et al.*, 2015). The most commonly used parameters to study the toxicity of atmospheric pollutants on lichens are chlorophyll degradation (Šujetovienė & Sliumpaitė, 2013; Balarinová *et al.*, 2014; Karakoti *et al.*, 2014; Šujetovienė, 2015) and lipid peroxidation (Paoli *et al.*, 2015; Šujetovienė *et al.*, 2019). Like all other plant components, including chlorophyll, polyphenols also respond differently to pollutants in the air. Plants use phenolic compounds to defend themselves from oxidative stress brought on by a variety of airborne pollutants (Nobile *et al.*, 2021). Plant polyphenols have the property of naturally acting as antioxidants and being only mildly harmful. Exposure to abiotic stress triggers the accumulation of amino acids and amines in different plant species. Soluble sugars play a crucial role in a variety of metabolic processes, acting as a signal to control gene expression in photosynthesis, osmolyte production, and sucrose metabolism (Khan *et al.*, 2020). Proline, on the other hand, is crucial for plants; it protects them from various stresses and helps their faster recovery from stress (Mundada *et al.*, 2021).

Plants manufacture many enzymatic components, such as catalase (Lei *et al.*, 2022), and non-enzymatic components, such as glutathione (Hasanuzzaman *et al.*, 2020) to prevent ROS-induced damage, and change their protein composition (Amnan *et al.*, 2022). In response to abiotic stress, plants also produce H<sub>2</sub>O<sub>2</sub> as one of the ROS (Zhang *et al.*, 2022b). GSH levels grow in plants under stressful situations (Nahar *et al.*, 2017), and it is used as an adaptive mechanism for battling and tolerating stress (Gong *et al.*, 2018). Catalase activity also increases in plant under fluoride stress correlating with high concentration (Sharma & Kaur, 2019) and with exposure time (Sharma *et al.*, 2019).

Most studies showed the importance of the use of lichens as bioindicators of air pollution generated by heavy metals and the toxic effect generated follows the accumulation of these pollutants at the cellular level. However, few studies have conducted the toxic effect induced by fluoride on lichens, for this purpose the current review will shed some light on the fluoride-induced toxic effects in lichens and the adaptation mechanisms used by lichens to combat induced toxicity.

## 2. GENERAL DATA ON LICHENS

### 2.1. History and Definition

Lichenology is a branch of biology that is interested in the study of lichens. It is a discipline covering several aspects of these organisms: taxonomy, morphology, physiology, the algae-fungus relationship, ecology, and bio-indication (Kranmer *et al.*, 2009). The term lichen is of Greek origin (hence its pronunciation likèn), it was found for the first time in the writings of THEOPHRASTE (IV century before our era) who also designates the plants growing on the trunks of trees (Ozenda & Glauzade, 1970). The use of lichens as bioindicators and bioaccumulators has been studied for several years, the first study was carried out by William Nylander (1822-1899) who published an article in 1866 (Les lichens du Jardins du Luxembourg) in which he studied the relationship between environmental pollution and the disappearance of several lichen species (Vitikainen, 2009).

Lichens have long been thought of as composite organisms made up of algae and/or cyanobacteria (phycosymbiont) hosted in a mutualistic relationship by a fungus (mycosymbiont): (1) Phycosymbiont (algae): it ensures the carbon supply of the whole by its assimilating pigments, (2) Mycosymbiont (The mushroom): thanks to the felting of its filaments, it provides support to the algae and prevents its dehydration. It represents more than 90 % of the lichen biomass. Within the lichen thalli, several algae species, yeasts, and even viruses have all been gradually found (Morillas *et al.*, 2022).

## 2.2. Lichen Morphology

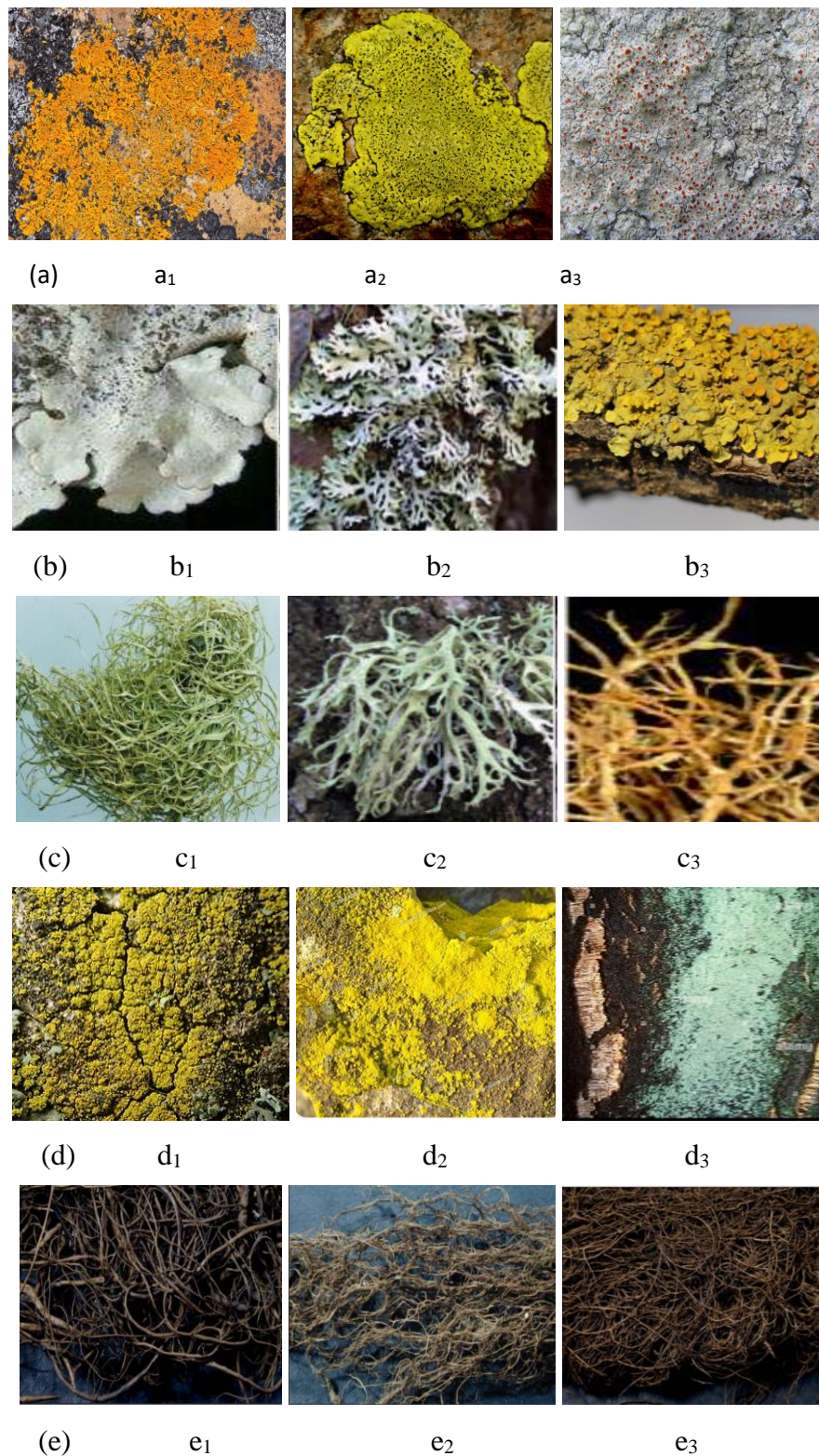
Lichens are thallophytes, their vegetative apparatus is a thallus representing neither leaves, nor stems, nor conductive apparatus and carrying the reproductive organs, the thallus of lichens have very varied forms among which we distinguish several major morphological types (Ozenda, 2000). The fungus partner is principally responsible for determining the three main growth types of thallus structures: foliose, fruticose, or crustose. Foliose and fruticose lichens are only partially attached to the substrate through anchor-like structures like rhizines and hapters, whereas, crustose lichens, which lack the lower cortex, are entirely attached (Büdel & Scheidegger, 2008). The phytobiont and its close physical contact with the mycobiont have a significant impact on the shape of the lichenized thallus. There are five different types of lichen thalli (Figure 1).

### 2.2.1. Principal type of lichen thalli

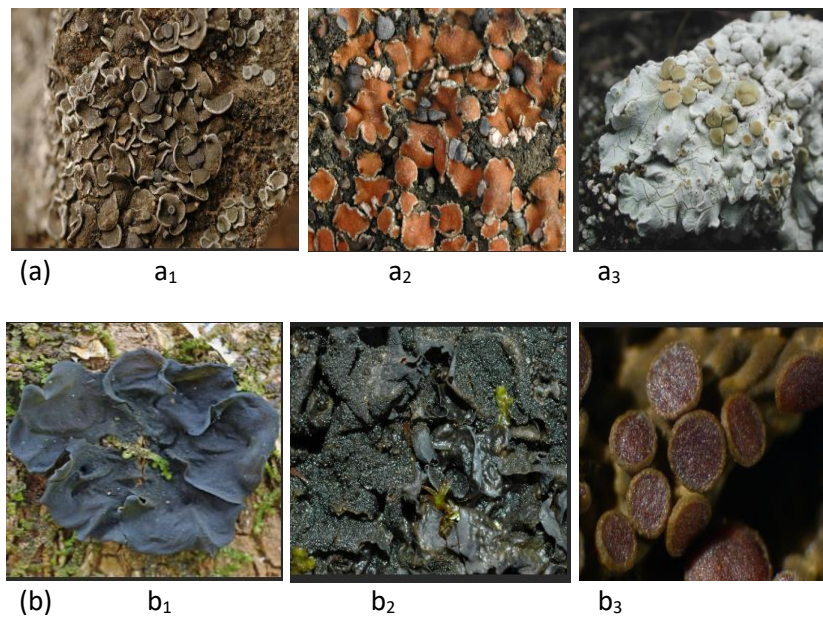
Lichens are in the form of: (1) Crustose thalli: Phytobiont in a distinct layer below an upper mycobiont cortical layer with no lower cortex, forming a crust closely adherent to the support (bark, rocks or earth), it is by far the most numerous (more than 4/5 of the lichens). The thallus is generally inseparable from the support. Example: *Lecanora*, *Pertusaria*, *Ochrolechia*; (2) Leprous thalli: Groups of phycobiont surrounded by mycobiont, result from a coherent association of granules (0.1-0.2 mm) each consisting of a bunch of hyphae associated with a few algal cells. Example: *Leparia*. (3) Foliose thalli: Phycobiont in a layer under an upper cortex with a discrete cortex underneath, in the form of lobes easily separable from the substrate to which they are sometimes attached by rhizines. Example: *Parmelia*, *Physia*, *Xanthoria*; (4) Filamentous thalli: Phycobiont surrounded by a sheath of mycobiont possessing the appearance of pads, they are in the form of very fine filaments, tangled and spread on the support. Example: *Usnea sp.*; (5) Fruticose thalli: Shrub; erect, vertical or dragging; radial structure, often attached to the base, with the phycobiont in a layer inside the outer cortex, either tufts hanging from the trunk or branches of trees, or tufts of stems. Example: *Usnea*, and *Ramalina* (Elkhateeb *et al.*, 2022).

### 2.2.2. Other thalli

Lichen thalli can be presented in three other forms (Figure 2): (1) Gelatinous thalli: These are the ones that contain cyanobacteria. The thallus is in the form of a simple structure with little differentiation. Example: *Collema*, *Epebe*, *Lichina*, *Placodium*, *Leptogium*; (2) Squamulose thalli: They are intermediate thalli between crustose and foliose thalli, are found in the form of more or less close together or overlapping scales, on board not adhering to the support. Example: *Psoradeciopen*, *Hypocenomycescalaris*, *Normaninapulchella*; (3) Composite thalli: The composite thallus is a component of two thalli: the first is crustose, squamulose thallus or foliose, more or less spread out on the substrate. The second of a fruticose nature, growing perpendicular to the substrate. Example: *Cladonia* (Büdel & Scheidegger, 1995).



**Figure 1.** Growth-forms and general appearance of principal type of lichen thalli; (a): Crustose lichens (a<sub>1</sub> : *Lecanora* sp., a<sub>2</sub> : *Rhizocarpon geographicum*, a<sub>3</sub> : *Haematomma puniceum*) (b): Foliose lichens (b<sub>1</sub>: *Parmelia*, b<sub>2</sub>: *Hypogymnia*, b<sub>3</sub>: *Xanthoria*), (c): Fructicose lichens (c<sub>1</sub>: *Usnea*, c<sub>2</sub>: *Ramalina*, c<sub>3</sub>: *Teloschistes*), (d): Leprose lichens (d<sub>1</sub> : *Candelariella efflorescens*, d<sub>2</sub>: *Chrysothryx candelaris*, d<sub>3</sub> : *Lepraria incana*), (e): Filamentous lichens (e<sub>1</sub>: *Bryoria fremontii*, e<sub>2</sub>: *Bryoria fuscescens*, e<sub>3</sub>: *Bryoria pseudofuscescens*) (Alison, 2006; Nimis *et al.*, 2017).



**Figure 2.** Growth-forms and general appearance of squamulose and gelatinous lichens; (a): Squamulose lichens (a<sub>1</sub>: *Toninia auriculata*, a<sub>2</sub>: *Psora decipiens*, a<sub>3</sub>: *Squamarina lentigera*), (b): Gelatinous lichens (b<sub>1</sub>: *Collema subflaccidum*, b<sub>2</sub>: *Collema flaccidum*, b<sub>3</sub>: *Collema nigrescens*) (Nimis *et al.*, 2017).

### 2.3. Lichen Ecology

Lichens can develop on a variety of substrates and in a variety of weather situations: **(1)** Corticolous lichens are those that grow on tree trunk and bark; **(2)** Ramicolous lichens live on twigs; **(3)** Lignicolous lichens live on wood; **(4)** Saxicolous lichens live on rocks and boulders; **(5)** Muscicolous lichens live on moss; **(6)** Terricolous lichens live on soil; **(7)** Foliicolous lichens live on evergreen leaves (epiphyllous). Any lichen that grows on another plant is generally referred to as epiphytic (Singh *et al.*, 2016).

### 2.4. Lichen Reproduction

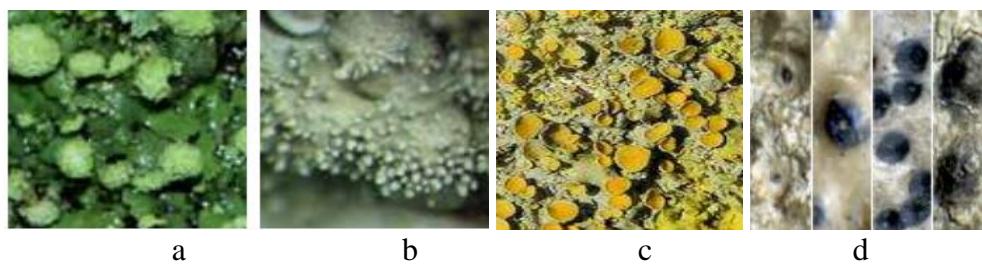
Lichens frequently combine sexual and vegetative reproduction. Vegetative means can simply involve thallus fragmentation or specialized organs like soredia or isidia. The fungal partner is often the sole one involved in sexual reproduction, and the variety of fruiting bodies or ascomata (sing. ascoma) is astounding. Not only that, but they also differ considerably among species and higher taxonomic levels like genus and family in terms of internal architecture such as tissue arrangement, spore sacs (known as asci), and the spores themselves (Perlmutter, 2009).

#### 2.4.1. Vegetative reproduction

The lichen complex can spread globally, either in the form of thallus fragments, or through the set of special organs, soralia and isidia (Figure 3). A soralia is a crack in the cortex (formed by the fungus) at the level of the medulla of the lichen which resolves into a floury dust of soredia which are glomeruli formed of a few cells of algae surrounded by a bunch of hyphae of very small size and easy dispersal. While the isidia are small buds carried on the surface of the thalli, these isidia, which are heavier than the soralia, cannot be transported as far, they rather ensure colonization of the substrate, they are generally considered as organs of multiplication (Ozenda, 2000).

#### 2.4.2. Sexual reproduction

It is carried out by the production of spores of the fungus, which, by germinating then give hyphae which capture the algae. Indeed, two sexually differentiated fungal hyphae merge and give the surface of the thallus structures in the form of buttons (apothecia), or more or less closed cups (perithecia) (Figure 3), in which specific cells (asci) will develop ascospores (generally 8 spores per ascus but the number can vary, and post-miotic mitoses make it possible to obtain in certain cases 32, 64, ... ascospores, or much less) (Honegger, 1998).



**Figure 3.** Organs for vegetative and sexual reproduction; a: soredia, b: isidia, c: apothecia, d: perithecia (Nimis *et al.*, 2017).

## 2.5. Composition of Lichen Substances

Primary and secondary lichen compounds can be separated into two categories: Primary lichen compounds play structural and metabolic roles in biological processes. The majority of these are found in other plants. Lichens create a wide variety of peculiar secondary products that are not present in other plants. The functions of secondary lichen compounds are still not fully understood. They most likely function as antibiotics (acids), photosynthesis-related molecules (atranorin), light filters (parietin), or agents that speed up the transfer of carbohydrates from the photobiont to the mycobiont or have roles in degrading the mineral substrates (Podterob, 2008). Lichen metabolites act as a major factor in the metal homeostasis and pollution tolerance of lichen (Bhattacharyya *et al.*, 2016).

### 2.5.1. Primary metabolites

Primary metabolites include proteins, amino acids, lipids, carbohydrates, polyols, carotenoids, vitamins, and other organic compounds vital to lichen metabolism and structure (Elix & Stocker-Wörgötter, 2008; Mitrović *et al.*, 2011).

### 2.5.2. Secondary metabolites

A wide variety of chemical groups are represented in lichen secondary metabolites (Nayaka & Haridas, 2020), such as aliphatic acids, sugar alcohols, quinines, chromones, xanthenes, dibenzofurans, depsides, depsidones, depsones, terpenoids, steroids, carotenoids, and diphenyl ethers (Yousuf *et al.*, 2014). Secondary metabolites are produced by mycobionts, which then store them in the cortex or the medullary layer (Calcott *et al.*, 2018).

## 2.6. Uses of Lichens

### 2.6.1. Medicinal uses of lichens

In traditional medicine, several lichens such as *Usnea*, *Evernia*, *Cetraria*, *Cladonia*, *Ramalina*, *Lobaria*, *Peltigera* and *Xanthoparmelia* are most frequently used by cultures across the world, particularly in temperate and arctic regions to treat wounds, skin problems, respiratory, and obstetrical difficulties. They have been used for both their carbohydrate and secondary metabolite contents (Crawford, 2015). Likewise, due to their bioactive compounds, lichens are used as antimicrobial and antioxidant agents (Elkhateeb *et al.*, 2021) also as antiviral agent (Bhattacharyya *et al.*, 2016). Currently, lichens are employed to treat a variety of human illnesses because of their anti-cancer, antigenotoxic, anti-inflammatory, analgesic and antipyretic activity (Nugraha *et al.*, 2019; Šeklić *et al.*, 2022). In addition, the lichen's metabolites are being tested for their potential as hepatoprotective, cardiovascular protective, gastrointestinal protective, antidiabetic, and probiotic agents (Nayaka & Haridas, 2020).

### 2.6.2. Uses of lichens as food

Because of its richness in polysaccharides, certain enzymes and some vitamins, some lichens serve as important source of food for animals (*Cladonia rangiferina*, *Cetraria islandica*, species of *Stereocaulon*, *Evernia*, *Parmelia* and *Lecanora*) and humans during famine (*Parmelia* species, *Lecanora esculenta*, *Cetraria islandica*, *Lecanora esculenta*, *Umbilicaria esculenta*) (Elkhateeb *et al.*, 2022).

### 2.6.3. Uses of lichens for mineral production

Lichens living on rocks can pull oxalate and turn it into oxalic acid, particularly calcium oxalate monohydrate and calcium oxalate dihydrate (Marques *et al.*, 2016).

### 2.6.4. Uses of lichens as bioindicators of air pollution

The possibility that lichens are sensitive to air pollution was suggested as early as 1866 from observations made around Paris, France. Since then, several studies have been carried out in large urban areas on several continents, whose gaseous substances most involved in the decline of lichens appear to be sulphur dioxide which mainly affects the algal component by disrupting the process of photosynthesis and various fluorine compounds (Weaver, 1975). Because they are sensitive to changes in temperature, air pollution, and water availability, lichens are excellent markers of planetary change (Bajpai *et al.*, 2018). Their biodiversity is substantially impacted by even minor environmental changes (Eldridge & Delgado-Baquerizo, 2018). According to the researchers, urbanization and environmental pollution appear to have an impact on every functional aspect of lichens (Koch *et al.*, 2019).

They are used in the bio indication of air quality (Kuldeep & Prodyut, 2015; Pescott *et al.*, 2015; Sulaiman *et al.*, 2018; Benítez *et al.*, 2019; Mohamed *et al.*, 2020; Quijano-Abril *et al.*, 2021). Lichens are capable of absorbing large amounts of trace elements from the atmosphere (Caggiano *et al.*, 2015; Darnajoux *et al.*, 2015). Additionally, they serve as biomonitors (Kularatne & de Freitas, 2013; Ite *et al.*, 2014; Conti & Tudino, 2016; Demková *et al.*, 2017; Abas, 2021; Tarawneh *et al.*, 2021) and bioaccumulators of heavy metals (Węgrzyn *et al.*, 2016; Winkler *et al.*, 2019; Rola, 2020; Vannini *et al.*, 2021). They can develop on challenging supports, like coastal rocks (Dévéhat *et al.*, 2014), and are distinct from the majority of other eukaryotic species in terms of their physiology, anatomy, and capacity to tolerate extreme stresses (Expósito *et al.*, 2022). Despite their distribution and diversity are influenced by climate, soil chemistry and geography (Škvorová *et al.*, 2022), lichens can resist various stressful conditions such as extreme drought and temperatures (Beckett *et al.*, 2021), salinity (Chowaniec & Rola, 2022), heat (Kraft *et al.*, 2022), nutrient deficiency (Hauck *et al.*, 2009) heavy metals (Rola, 2020) and fluoride (Roberts & Thompson, 2011). These stresses are the source of ROS and the most important adaptation mechanism used by lichens for tolerance to stressful conditions is the scavenging of these ROS (Kranner *et al.*, 2009). Lichens can also exhibit typical stress-tolerant characteristics, such as reduced growth rates, significant longevity, low nutrient requirements, the presence of specific morphological and physiological adaptation, and changes in ecological behavior for surviving in the most hostile environments in the world (Armstrong, 2017).

## 3. GENERAL DATA Fluorine

### 3.1. History and General Properties of Fluorine

After the discovery of sodium and potassium by the English chemist Humphrey Davy (1778-1829), André-Marie Ampère (1775-1836) grasped the idea that chlorine and fluorine were both chemical elements but did not publish his hypotheses. He pointed to the analogies between hydrochloric acid and hydrofluoric acid and concluded that an element first called oxy-fluoric and then fluorine must exist. On 1<sup>st</sup> November 1810, André-Marie Ampère even suggested the possibility of isolating the element fluorine by electrolysis of anhydrous hydrofluoric acid. In 1813, he announced that a new element had been discovered (Moissan, 1886).

Fluorine, the most electro-negative element of the halogen group, its electronegativity in the Pauling scale is 4 against 3.5 for O<sub>2</sub> and 3 for Chlorine. Fluorine is a chemical element with the atomic number 9 and is represented by the symbol F. At ordinary temperature and pressure, fluorine gas is an elemental form of the element fluorine. F<sub>2</sub> is the formula for fluorine gas. Fluorine gas doesn't exist freely in nature due to its high reactivity. Fluorine combines directly with all elements other than oxygen and nitrogen, reacts vigorously with most oxidizable substances and organic compounds, which explains its toxicity (Chappuis, 1991).

### 3.2. Sources of Fluoride

Parent rock is the main natural source of inorganic fluorides in the soil. Fluoride is naturally released into the environment by mineral weathering, volcanic emissions, and marine aerosols (Fuge, 2018). Different industrial uses exist for inorganic fluorine compounds. Fluoride is a chemical that is used in the manufacturing of aluminum, as a flux in the production of steel and glass fiber, and as a waste product that is released into the air, water, and land. Additionally, it may be discharged into the environment during manufacturing phosphatic fertilizers, bricks, tiles, and ceramics (Bonvicini *et al.*, 2006; Walna *et al.*, 2007).

### 3.3. Fluorine and Main Derivatives

#### 3.3.1. Gaseous mineral compounds

Gaseous forms of fluorine include: **(1) Fluorine**: a yellow-green gas at ordinary temperature, (fluorine 18) prepared in nuclear reactors and used in animal experiments (Chappuis, 1991); **(2) Hydrogen fluoride**: also called hydrofluoric acid, it is the fluorinated compound whose industrial production is the most important, it is a strong corrosive chemical that can cause intense irritation, severe burns and necrosis (eye, lung, digestive tract) (Kim and Su, 1999); **(3) Silicified fluorine derivatives**: also called silicon tetrafluoride ( $\text{SiF}_4$ ): is a very toxic gas, industrial pollutant of many industries (coal combustion, aluminum industry, superphosphate plant, brickworks, tile works, glassworks...),  $\text{SiF}_4$  is also observed in terrestrial volcanic gases and is predicted to be the major F-bearing species in low-temperature (Schaefer & Fegley, 2005).

#### 3.3.2. Fluorides

The main forms of fluorides are: **(1) Alkaline fluorides** such as calcium fluoride ( $\text{CaF}_2$ ), strontium fluoride ( $\text{SrF}_2$ ), Barium fluoride ( $\text{BaF}_2$ ), magnesium fluoride ( $\text{MgF}_2$ ), lithium fluoride ( $\text{LiF}$ ) and sodium fluoride ( $\text{NaF}$ ) (Song and Williams, 1993). Except  $\text{LiF}$ , all alkaline fluorides are soluble in water. The most common alkaline fluoride is  $\text{NaF}$  responsible for most accidental or voluntary poisoning by the fluoride ion (confusion with edible compounds, ingestion of insecticides, fungicides ...). In addition,  $\text{NaF}$  has a detrimental effect on immunity and humoral immunity by causing the reduction of the population of T and B lymphocytes (Kuang *et al.*, 2016); **(2) Main mineral forms**: such as fluor spar ( $\text{CaF}_2$ ), Cryolite ( $3\text{NaF}, \text{AlF}_3$ ) and Fluorapatite [ $3\text{Ca}_3(\text{PO}_4)_2, \text{CaF}_2$ ] constituting phosphate rocks and frequently responsible for endemic fluorosis (Choudhary *et al.*, 2019).

#### 3.3.3. Organic fluorine compounds

In recent decades, scientists have become interested in organic fluorine compounds. This is owing in significant part to their ubiquitous use in medicines, agrochemicals, and functional materials (Li *et al.*, 2018) like: **(1) Chlorofluorocarbons (CFCs)**, commonly referred to as Freon, generally non-toxic. These are gases or more rarely liquids used as refrigerants, solvents and, until recent years, as aerosol propellants (Mishra *et al.*, 2022); **(2) Fluorocarbons**: characterized by a high gas-dissolving capacity (oxygen, carbon dioxide, inert gases), low viscosity, and chemical and biologic inertness. The reason why they are used therapeutically as oxygen transporters instead of hemoglobin (van Hulst *et al.*, 2008); **(3) Fluorinated anesthetics**: widely used as an anesthetic agent, these are enflurane, isoflurane, sevoflurane, methoxyflurane, and fluorinated hydrocarbons such as halothane (Chen *et al.*, 2015).

#### 3.3.4. Natural organic compounds

They are rare, including fluorooleic acid and fluoroacetic acid found in some plants. After ingestion, fluoroacetate is rapidly converted to the more toxic fluorocitrate (Talcott, 2018), while sodium fluoroacetate, very toxic, is used as a rat poison (Goncharov *et al.*, 2020).

### 3.4. Use of Fluorine

Fluorine is a trace element since it represents only 0.0037 % of the human body, to do this, it is beneficial for human health in low concentrations, but is toxic in excess (Fordyce, 2011).



### 3.4.1. Caries and periodontal disease

The beneficial effect of fluoride derivatives in the prevention of tooth decay has been known since 1930, fluoridation of water or salt prevents tooth decay at the communal level as well as on an individual level through use at home and professional application (Pollick, 2018). Low levels of NaF exhibit a pharmacological role in the inflammatory response against the development and progression of periodontal disease (Kim *et al.*, 2019).

### 3.4.2. Therapeutic use of fluorine

Fluorouracil is used to treat actinic and solar keratosis, as well as carcinomas of the head and neck, colon, rectum, breast, stomach, bladder, and pancreas (Vardanyan & Hruby, 2006). Fluorine has a significant impact on the hydrophobic contact between the drug molecule and the receptor because of its ability to make the molecule more lipophilic, for this reason the fluorine atom is used in the production of several therapeutically helpful medications combating numerous life-threatening disorders (Gupta, 2019).

Fluorinated molecules are widely used in bioengineering and nanotechnology due to its properties in forming C-F bonds, which can adapt membrane permeability and improve the pharmacokinetic properties of drugs (Zhang *et al.*, 2022a). The most common example of fluorination is that of fluorination of steroids, this one has been very remarkable especially in the anti-inflammatory field, this is the case of 9 $\alpha$ - and 6 $\alpha$ - fluorosteroids used in the treatment of rheumatoid arthritis and fluticasone propionate used as an anti-inflammatory in allergic rhinitis and asthma (Filler & Saha, 2009; Yamazaki *et al.*, 2009).

### 3.4.3. Prevention of osteoporosis and otosclerosis

Once bone has been destroyed, fluoride offers the greatest potential as an osteoporosis treatment, essentially common postmenopausal osteoporosis (Pak *et al.*, 2009). In 1961, Rich and Ensinck employed sodium fluoride for the first time to treat osteoporosis (Kleerekoper, 1998). According to low-quality study, patients with otosclerosis may benefit from sodium fluoride to retain hearing and lessen vestibular symptoms (Cruise *et al.*, 2010).

## 3.5. Toxicokinetic of Fluorine

Fluorine absorption can be done by: **(1)** Inhalation exposure: specific for hydrogen fluoride or mixtures of hydrogen fluoride and fluoride, this type of exposure is one of the industrial accidents that causes serious damage (Lee and Jeong, 2021); **(2)** Oral exposure: the gastrointestinal system easily absorbs soluble fluoride compounds such as sodium fluoride, hydrogen fluoride, and fluorosilic acid (Whitford, 1996), about 80 to 90 % of fluoride ingested through this route by passive diffusion (Zohoori & Duckworth, 2017); **(3)** Dermal exposure: the rapid entry of fluoride ions into the epidermis by hydrofluoric acid results in soft tissue necrosis, decalcification, and bone deterioration (Dennerlein *et al.*, 2016). Accidental cutaneous exposure to anhydrous hydrogen fluoride has been associated with systemic fluoride poisoning. After ingestion, fluorides pledge the plasma with maximum absorption within 60 minutes of exposure initiation (Buzalaf & Whitford, 2011). Once in the blood plasma, fluoride is distributed, to soft and mineralized tissues and reversibly incorporated mainly in bone, being released back to plasma during bone remodeling (Ekstrand, 1996; Whitford, 1996).

About 60 % of fluoride that has been ingested by healthy adults is eliminated in urine via the kidneys, compared to about 45 % for children (Villa *et al.*, 2010; Buzalaf & Whitford, 2011). Most of the fluoride not absorbed from the stomach is absorbed from the small intestine and eliminated in feces (Buzalaf & Whitford, 2011). Fluoride is also excreted in sweat (Fawell *et al.*, 2006), and saliva (Ingram *et al.*, 2005).

## 3.6. Toxic Effects of Fluorine

Due to the excessive intake of fluoride through drinking water, fluoride toxicity adversely affects physiological and biochemical parameters in either agricultural crops, plants, animals, or human consumption (Tak, 2018).

### 3.6.1. Toxic effects on the environment

The use of chlorofluorocarbons (CFCs) as aerosol propellants expected to decrease and even disappear due to the action of freon components on atmospheric ozone (Mishra *et al.*, 2022). Fluorinated gases (F-gases) used as refrigerants, blowing agents and electrical insulators are powerful greenhouse gases and, therefore, their release into the environment creates a significant contribution to global warming (Sheldon & Crimmin, 2022).

### 3.6.2. Human toxicity

Fluoride has recently been grouped with hazardous metals (lead, methylmercury, arsenic) and polychlorinated biphenyls in epidemiological research, because of their adverse effects obtained in animal experiments, in particular on developmental toxicity, and the molecular mechanisms by which it can cause effects. Given the extensive fluoridation of drinking water and the ubiquitous use of fluoride in dental hygiene products like toothpaste, if this evaluation is accurate, it would be quite pertinent (Guth *et al.*, 2020). Acute Toxicity may be caused by accidental ingestion or, for suicidal purposes, of sodium fluoride, fluorosilicate, hydrofluoric acid or fluorosilic acid solutions, the symptoms of which are vomiting, diarrhea, salivation, respiratory arrest, cardiac depression, convulsions, and leading coma (Norman & Arden, 1991).

Dental fluorosis is among the most well-researched long-term effects of fluoride in people (EFSA, 2013). Indeed, excessive incorporation of fluoride into tooth enamel before teeth eruption leads to hypomineralization of developing teeth. This problem is found when fluoride intake exceeds a concentration in drinking water of approximately 1 mg/L of fluoride, under conditions where drinking water is the only relevant source of fluoride. Another example of the long-term effects of fluoride is skeletal fluorosis (osteosclerosis and other bone abnormalities) caused by persistent fluoride toxicity, which results in excruciating pain and weakness, due to exposure to the environment or industry (Choubisa, 2021; Mohideen *et al.*, 2022).

Higher doses of fluoride (> 10 mg/L) can be correlated with debilitating fluorosis and carcinogenic risk. Confined studies suggest that fluoride may speed up the development of cells that would eventually turn cancerous, but this claim is debatable because there is no conclusive evidence linking fluoride to the influence of carcinogenicity (Bajpai, 2013; Ali *et al.*, 2019). It should be mentioned that fluoride ions exhibit a number of genotoxic characteristics and may possess mutagenic effects when in prolonged contact with biological components, but there are only a few studies discussing the ability of fluoride ion to increase the level of genotoxic effects. The danger of genotoxicity associated with human exposure with fluoride compounds is still an open question (Ribeiro *et al.*, 2017; Mikheeva *et al.*, 2020)

### 3.6.3. Fluoride phytotoxicity

One of the most phytotoxic chemical elements for plants, fluoride is present in many environmental matrices and can be harmful to them even in small amounts (Banerjee & Roychoudhury, 2019). Fluoride can cause slower plant growth and browning of their leaves, generally poisoning begins with chloroses, followed by the destruction of tissues, color change and finally the appearance of necrosis. The most remarkable toxic effect of fluoride on plants is leaf damage (Figure 4); indeed, plant leaves are the site of fluorine accumulation which causes stomata closure and inhibition of photosynthesis, hence the appearance of necrosis. Fluorides also induce degradation of photosynthetic pigments, thereby inhibiting photosynthesis, interfere with active metabolism, decrease the rate of cell division and expansion which decreases the germination and development of seed (Ram *et al.*, 2014; Sharma and Kaur, 2018; Choudhary *et al.*, 2019; Pelc *et al.*, 2020; Sahariya *et al.*, 2021), length of root, length of shoot, plant height, number of leaves, size of leaf, number of flowers per plant and fruit-set percentage (Singh *et al.*, 2013; Sodani *et al.*, 2021). Fluoride toxicity also has an adverse effect on development, mineral nutrition, respiration, reproduction, and the activity of cellular enzymes (Sahariya *et al.*, 2021).



**Figure 4.** Leaf spots due to fluorine toxicity (Chatterjee *et al.*, 2020).

### 3.6.4. Toxic effects of fluoride on lichens

Fluorinated pollution can cause an almost total disappearance of some lichen species. A precise cartographic study makes it possible to establish the existence of a lichen desert in the immediate vicinity of the factories. As one moves away from it, the lichen flora gradually enriches (Perkins, 1992). Numerous studies have shown a relationship between lichen damage and fluoride accumulation. This is because lichens are able to quickly accumulate large amounts of fluoride. This accumulation varies according to the lichen species, the time and the distance from the source of pollution (Deruelle & Lallement, 1983), climatic factors (Conti & Cecchetti, 2001), and fluoride concentration (Chakrabarti *et al.*, 2014).

As a result of the stressful environment, lichens suffered numerous biochemical and physiological alterations. The most prevalent metric used to study the toxicity of air pollutants on lichens is chlorophyll degradation (Šujetovienė, 2015). Fluoride has the greatest impact on photosynthesis and respiration (Sharma & Kaur, 2018). Significant decrease in chlorophyll a, chlorophyll b and total chlorophyll contents in *Xanthoria parietina* under fluoride stress was noted by Benhamada *et al.* (2023b), however significant increase of chlorophyll a/b ratio was obtained correlating with exposure time to NaF ( $r = 0.818$ ,  $p < 0.001$ ), indicating that chlorophyll b is more affected than chlorophyll a in *X. parietina*.

In *X. parietina* under fluoride-induced stress, the color change of the pinkish gray thalli suggests that it is accompanied by a destruction of lichenic acids, this is due to the destruction of chlorophylls a and b, and transformation into phaeophytin, before the complete degradation of all pigments including carotene and xanthophyll (Deruelle & Lallement 1983; Zhang *et al.*, 2016; Yang *et al.*, 2019). Fluoride accumulation would also create favorable conditions for exosmosis causing permanent plasmolysis of lichen algal cells. This phenomenon of plasmolysis is explained by the inhibition of the metabolism of the cell wall compounds, there will be a slight dehydration resulting in the folding of the lichen upper cortex, including the necrosis formation (Figure 5). According to Nash III (1971) and Gilbert (1973), this necrosis is due to the destruction of lichenic acids.



**Figure 5.** Fluoride injury symptoms (necrosis) in epiphytic lichens (LeBlanc *et al.*, 2011).

Fluoride also decreases germination of spore. Semadi (1989) studies have shown that low concentrations of NaF inhibit spore germination in *Physonia pulverulacea* lichen. Plants boost the activity of antioxidant enzymes such as catalase in order to trap ROS and detoxify their effects (Lei *et al.*, 2022). Several studies have shown that catalase expression increases significantly correlating with increasing concentrations (Mondal, 2017; Elloumi *et al.*, 2017;

Sharma & Kaur, 2019; Benhamada *et al.*, 2023b) and with increasing exposure time to sodium fluoride (NaF) (Sharma *et al.*, 2019).

Several studies have found that lichens employ glutathione for detoxification; GSH increases in plants under stressful situations and is part of plant adaptation methods to battle and survive stress (Sanità di Toppi *et al.*, 2008; Nahar *et al.*, 2017; Gong *et al.*, 2018). Results obtained by Benhamada *et al.* (2023b) showed that the GSH content increases correlating with increasing concentrations of NaF in *X. parietina*. During lipid peroxidation, a wide range of aldehydes are produced, including MDA. MDA is a promising biomarker and diagnostic for lipid oxidative damage in drought-stressed plants (Amine-Khodja *et al.*, 2022; Toto *et al.*, 2022). Compared to the control test, results obtained by Benhamada *et al.* (2023a) showed a significant increase in MDA contents ( $p < 0.05^*$ ) in exposed *X. parietina* to NaF solutions. Similar results were archived by Dzubaj *et al.* (2008) and Pisani *et al.* (2009) who showed that *X. parietina* reacts against fluorine by increasing MDA content.

Proline is part of a broader adaptive response to adversity (Liang *et al.*, 2013; Ghosh *et al.*, 2022). Proline accumulation might be thought of as a stress indicator that changes depending on the plant type (Amine-Khodja *et al.*, 2022). According to Benhamada *et al.* (2023a), a significant increase in proline content in *X. parietina* was noted correlating with increasing exposure time to NaF concentrations ( $r = 0.783$ ,  $p = 0.00032$ ). Soluble sugars and polyphenols like proline, are part of plant adaptation strategies to battle and tolerate stressful situations (Gangola & Ramadoss, 2018; Khan *et al.*, 2020; Amine-Khodja *et al.*, 2022). Results obtained by Benhamada *et al.* (2022) showed significant increase in polyphenol contents correlating with increasing concentration of NaF in *X. parietina* thalli. Significant increase in the content of soluble sugars correlating with increasing concentration of NaF ( $r = 0.678$ ,  $p = 0.0010$ ) was also noted in *X. parietina* under NaF stress (Benhamada *et al.*, 2023a).

## 4. GENERAL DATA ON LEAD

### 4.1. Definition and History

Lead (Pb) from the “Latin plumbum” with atomic number 82 and atomic mass of 208, is a blue-gray non-radioactive metal that turns gray once exposed to air, with a melting point of 327.5 °C and a boiling point at atmospheric pressure of 1740 °C. It is the most universally widespread element of heavy metals and the second most toxic heavy metal after arsenic. Lead and its oxides typically create covalent bonds when reacting with acids and bases (Boldyrev, 2018). It has been commonly used for nearly 6000 years in human activities (Papanikolaou *et al.*, 2005), and since at least 200 B.C. humans have been aware of its harmful effects, indeed Asia Minor saw the earliest known usage of lead between 6000 and 4000 B.C. (Hernberg, 2000). Meanwhile and with the huge development of population and economic growth, lead pollution has increased from an estimated 10 tons to 1 000 000 tons per year, with a global production about ten million tonnes in 2014 (Boldyrev, 2018).

### 4.2. Origin of Lead

Lead occurs naturally in soil, water, plants and animals (Tiwari *et al.*, 2013). It is found naturally in the earth's crust at concentration of 15–20 mg/kg. In general, lead concentrations are around 5 to 25 mg/kg in soil, 1 to 60 µg in surface water, and around 1µg/m<sup>3</sup> in air (Lu, 1992). Lead can be emitted naturally either by erosion that carries it to the soil, surface water, and sediment, or by terrestrial or underwater volcanic eruptions (Popescu *et al.*, 1998). Industrial lead pollution originates from several industrial processes, especially from mining and smelting, plastics, printing and phosphate industries, manufacturing batteries, metallurgy, and lead refining complexes (Kapusta & Sobczyk, 2015; Kabir *et al.*, 2020) as well as car traffic and leaded aviation gasoline (Lin *et al.*, 2011).

### 4.3. Lead, Lead Compounds and Uses

(1) Metallic lead (Pb): lead is primarily used to create rechargeable storage batteries. Pb makes up the gray negative electrode in battery (Crompton, 2000); (2) Lead oxides: such as  $\alpha$ -PbO (litharge) and  $\beta$ -PbO (cutter) used in the industries of glassware, enamels, drying oils of accumulators,  $\alpha$ -PbO<sub>2</sub> (scrutinyite) and  $\beta$ -PbO<sub>2</sub> (plattnerite) used as energetic oxidants and make up the red color positive electrode in battery (Crompton, 2000), and Pb<sub>3</sub>O<sub>4</sub> (lead tetraoxide or minium) used in the composition of anti-rust paints (Pavlov, 2017); (3) Lead sulphides (PbS): formed by chemical reaction of lead acetate with thiourea at room temperature. It provides varnishes of yellow color, which can be colored brown by addition of manganese oxide or green by addition of copper oxide (Bhatt *et al.*, 2011); (4) Lead arsenate PbAH<sub>5</sub>O<sub>4</sub> and lead stearate Pb(C<sub>17</sub>H<sub>35</sub>COO)<sub>2</sub>: used in insecticides and herbicides (Gad and Pham, 2014); (5) Lead iodide PbI<sub>2</sub> and lead base acetate Pb(CH<sub>3</sub>-COO)<sub>2</sub>: used as a mordant in printing and dyeing textiles, as a lead coating for metals, as a dryer in paints, varnishes and pigment inks, and as a dye in hair dyes (Ghazi & Millette, 1964); (6) Alkyl derivatives of lead and organic lead compounds: such as tetraethyl lead and tetramethyl lead used as antiknock agents in gasoline (Filella & Bonet, 2017); (7) Lead nitrate Pb(NO<sub>3</sub>)<sub>2</sub>: used in the manufacture of matches and explosives, as a heat stabilizer in nylon, and as a coating on paper for photothermography (Nielsen, 2013); (8) Insoluble lead compounds: such as lead carbonate Pb(CO<sub>3</sub>)<sub>2</sub> and lead sulfate (PbSO<sub>4</sub>) used in paints synthesis (Nielsen, 2013), lead chromate (PbCrO<sub>4</sub>) used as a yellow pigment in paints, rubber, plastics, and ceramic coatings (Gad and Pham, 2014), lead fluoride (Pb<sub>3</sub>F<sub>8</sub>) used as a pigment in ancient Rome and in anti-corrosion coatings (Bose *et al.*, 1983) with additional uses in the electronic and optical industries, lead naphthenate used as catalysts and as a varnish drier, lead phosphate and lead stearate used as stabilizers in the plastics industry and lead sulfate with zinc in galvanic batteries (Nielsen, 2013).

### 4.4. Toxicokinetic of Lead

We distinguish respiratory absorption specific to small Pb inorganic lead particles and aerosols that can be almost completely absorbed, while larger particles can be moved by mucociliary clearance to the oropharynx and swallowed (James *et al.*, 1994); gastrointestinal absorption influenced by age (40–50 % for children compared to 3–10 % for adults), diet, nutrition and physiological characteristics of Pb in the ingested medium (Ziegler *et al.*, 1978) and dermal absorption specific for inorganic forms of lead but less frequent than inhalation and oral exposure.

Ingested lead undergoes the action of hydrochloric acid from gastric juice and that of bile secretions, which by determining partial solubilization and, consequently, increasing toxicity; absorption is maximum in the small intestine and duodenum. Once in the blood, lead mainly attaches to red blood cells before being distributed to the bones (Barry, 1981), lead can also be transferred from the mother to the fetus and also from the mother to infants via maternal milk (Papanikolaou *et al.*, 2005). Inorganic forms of lead are not metabolized, so they form complexes with a variety of proteins and non-protein ligands, while organic compounds are actively metabolized in the liver by oxidative dealkylation by cytochrome P-450 enzymes (Philip & Gerson, 1994). About 50 - 60 % of eliminated lead is carried out mainly through the urinary and biliary excretion route (Ziegler *et al.*, 1978), lead elimination can be also done through sweat, saliva, hair, nails, breast milk and seminal fluid (Barbosa *et al.*, 2006).

### 4.5. Lead Toxicity

#### 4.5.1. Human toxicity

Lead poisoning originates from paints, water, food, dust, but in the majority of cases by oral ingestion and absorption through the gut. Acute lead-related toxicity is manifested by headaches, muscle tremors, abdominal cramps, kidney damage, loss of memory with encephalopathy (Papanikolaou *et al.*, 2005). Lead exposure has a negative impact on the hematological, renal, reproductive, neurological, digestive and respiratory systems. Lead also

causes generation of ROS that results in critical damage to various biomolecules such as DNA, enzymes, proteins and membrane-based lipids, while simultaneously altering the antioxidant defense system (Wani *et al.*, 2015). Once in the blood, lead can inhibit certain enzymes responsible for heme synthesis, particularly  $\delta$ -aminolevulinic acid dehydratase (Sakai, 2000).

#### 4.5.2. Phytotoxic effects of lead

In plants, lead is mainly absorbed by the root system and in minor amounts through the leaves. Once inside the plant, lead accumulates in the roots, but part of it is transferred to the aerial parts. At the cellular level, it accumulates in the wall, vacuoles and forms small deposits in the endoplasmic reticulum (Sharma & Dubey, 2005). [Figure 6](#) shows an example of morphological distortion observed in the leaves of *Vicia faba* plants under lead stress.

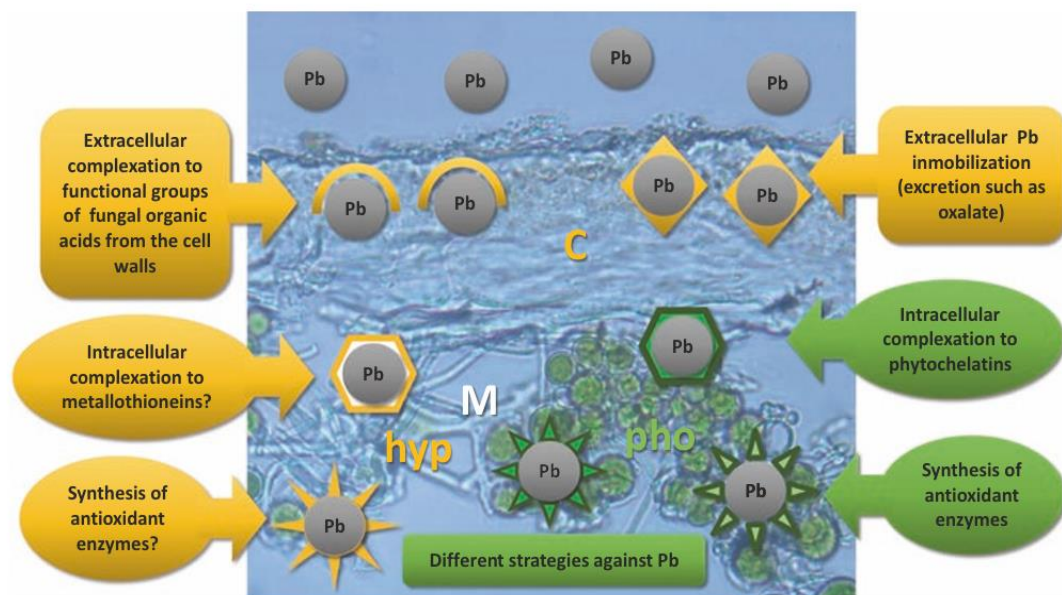
Lead toxicity causes severe oxidative damage to plants, it limits the synthesis of photosynthetic pigments, proteins, and affects net assimilation rate, sweat rate, and stomatal conductance (Arif *et al.*, 2019). Lead also reduces the rate of seed germination, and plant growth, and causes retardation of carbon metabolism, and blocks potassium in plants which causes membrane damage and stomatal closure (Zulfiqar *et al.*, 2019). Lead stress also inhibits the activities of several enzymes especially that of the Calvin cycle (Sharma & Dubey, 2005), reduces gas exchange attributes, and induces the oxidative stress markers and activities of antioxidant enzymes (Bamagoos *et al.*, 2022).



**Figure 6.** *Vicia faba* leaves grown on Hoagland nutrient solution under Pb stress, 0.0 mM (left) and 48 mM (right) (Kamel, 2008).

#### 4.5.3. Toxic effects on lichens

Foliose lichens are commonly utilized as biomonitors of metal contamination in the environment due to their proclivity to accumulate high quantities of dangerous metals (Subhashini & Suganthi, 2014; Purvis, 2014; Caggiano *et al.*, 2015; Darnajoux *et al.*, 2015). Lichens, according to Abas and Awang (2017), are good biological indicators for biomonitoring. *X. parietina* can accumulate substantial levels of heavy metals when compared to other fruticulous lichens such as *Ramalina farinacea* (Belguidoum *et al.*, 2021). Using a natural sensor for the sampling of biological material, the lichen *X. parietina* was capable of accumulating four heavy metals (Cr, Zn, Cu and Ni) in the Setif region, North-East of Algeria (Douibi *et al.*, 2015). Transplantation of lichen thalli of *Evernia prunastri* and *Ramalina farinacea* from an unpolluted site to a polluted site showed significant accumulation of lead after 3 months of exposure time (Šujetovienė & Česynaitė, 2021). Additionally, Benhamada *et al.* (2023c) verified that lead accumulation in *X. parietina* thalli is correlated with longer exposure times and higher lead nitrate concentrations  $\text{Pb}(\text{NO}_3)_2$ . Lead has been demonstrated to infiltrate cells, particularly in fungal cortical compartments, even though lichens still have significant extracellular quantities of the metal, primarily coupled to cell walls and extracellular polymers, once inside the cell, the first important sign of its toxicity is the reduction of photosystem II (PSII) photochemical reactions, and consequently the reduction of integrity and chlorophyll content (Branquinho *et al.*, 1997). Mechanisms of tolerance to lead in lichens are shown in [Figure 7](#).



**Figure 7.** Mechanisms of tolerance to lead in lichens. The mechanisms of tolerance to lead of the mycobiont are marked in yellow and those of the phycobionts in green. When there is more than one phycobiont, these may have different strategies against lead. Different microalgae are represented with different thicknesses and shade of greens. C cortex, M mycobiont, hyp hyphae, pho phycobiont (Expósito *et al.*, 2019).

Unlike fluoride which showed symptoms related to lesions in epiphytic lichens (Figure 5), the accumulation of heavy metals, with the exception of Cd, did not show significant morphological differences between stressed thalli and control (Šujetovienė *et al.*, 2019). In addition to the control test, *X. parietina* thalli were treated with  $Pb(NO_3)_2$  concentrations for 24, 48, and 96 hours, and total chlorophyll content was quantified as a direct effect of lead stress, chlorophyll levels fell as lead concentrations in solution increased; the lowest levels of this pigment were found in thalli treated with high quantities of lead, showing that Pb had a detrimental impact on chlorophyll a content (Carreras & Pignata, 2007; Benhamada *et al.*, 2023c). Aboal *et al.* (2008) discovered that a decrease in chlorophyll a/b ratio is an obvious marker of degradation caused by senescence or stress. Additionally, Bajpai *et al.* (2010) discovered that heavy metals (Zn, Cd, and Cu) cause physiological changes and inhibit photosynthesis even at very low concentrations, while lead causes a decrease in total chlorophyll and Ca/b ratio.

Protein content in *X. parietina* decreased significantly with increasing  $Pb(NO_3)_2$  concentrations ( $r = -0.790$ ,  $p = 0.0002$ ) (Benhamada *et al.*, 2023c). Esposito *et al.* (2012) and Chetia *et al.* (2021) discovered a decrease in total protein levels to correspond with Pb, Cd, Zn, Cu, Co, Ni, and Cr in lichens growing in different contaminated locations. Catalase levels in plants exposed to lead increase considerably, according to Abu-Muriefah (2015) and Khan *et al.* (2021). Several other research have found that heavy metals promote oxidative stress in biomarkers (Taiwo *et al.*, 2014; Batool *et al.*, 2018; Ullah *et al.*, 2021; Benhamada *et al.*, 2023c).

Lead causes membrane damage, especially through water loss and ion leakage (Expósito *et al.*, 2019), indeed, lipid peroxidation, which is one of the main consequences of prooxidant pollutants examined in thalli lichen, can cause these impairments (Álvarez *et al.*, 2015; Gurbanov & Unal, 2019). Indeed, membrane damage results in the degradation of its phospholipids which accumulate in the form of MDA residues (Zoungranian *et al.*, 2019). Benhamada *et al.* (2023a) found a positive correlation between MDA contents in *X. parietina* and increasing concentrations of  $Pb(NO_3)_2$  ( $0.865$ ,  $p = 0.000031$ ).

Lead has the ability to stimulate the formation of ROS (Kováčik *et al.*, 2018; Wieners *et al.*, 2018, Benhamada *et al.*, 2023c) that react with several vital biomolecules of the species causing serious morphological, metabolic and physiological abnormalities (Zoungran *et al.*, 2019). To neutralize and trap free radicals produced by lead, lichens accumulate polyphenols, usnic acids, cysteine and tripeptide glutathione, proline, soluble sugars, GSH and catalase (Kováčik *et al.*, 2017; Expósito *et al.*, 2019; Gurbanov & Unal, 2019).

Plants respond to stress by storing proline and soluble sugars in order to protect the structure of their macromolecules (Alhasnawi, 2019). Proline determination in lichens is an investigative method for various stress events. Benhamada *et al.* (2023a), showed significant increase in proline and soluble sugar contents correlating with exposure time of *X. parietina* thalli to lead nitrate ( $r = 0.811$ ,  $p = 0.00013$  and  $r = 0.780$ ,  $p = 0.00036$ , respectively).

## 5. CONCLUSION

Based on this literature search, we were able to conclude that fluoride must be categorized as one of the most toxic air pollutants, even though lead was more toxic than fluoride. This opens the field to further research comparing the toxicity of fluorine to that of heavy metals on various other ecosystems. It will be highly beneficial to conduct more research to identify the cellular, intracellular, and molecular sites of action of lead and fluorine as well as to find out what additional compounds this lichen has produced to counteract stressful environments. Several other studies will be requested to compare the toxicity of heavy metals with that of fluoride and thus to control the use of fluoride, particularly in drinking water disinfection processes.

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The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

## Authorship Contribution Statement

**Ouahiba Benhamada:** Investigation, resources, visualization, software, formal analysis, and writing original draft. **Nabila Benhamada:** Language revision. **Essaid Leghouchi:** Supervision and validation.

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## REFERENCES

- Abas, A. (2021). A systematic review on biomonitoring using lichen as the biological indicator: A decade of practices, progress and challenges. *Ecological Indicators*, 121, 107-197. <https://doi.org/10.1016/j.ecolind.2020.107197>
- Abas, A., & Awang, A. (2017). Air pollution assessments using lichen biodiversity index (LBI) in Kuala Lumpur, Malaysia. *Pollution Research*, 36(2), 241-248
- Aboal, J.R., Couto, J.A., Fernández, J.A., & Carballeira, A. (2008). Physiological responses to atmospheric fluorine pollution in transplants of *Pseudoscleropodium purum*. *Environmental Pollution*, 153(3), 602-609. <https://doi.org/10.1016/j.envpol.2007.09.002>
- Abu-Muriefah, S.S. (2015). Effects of Silicon on membrane characteristics, photosynthetic pigments, antioxidative ability, and mineral element contents of faba bean (*Vicia faba* L.)



- plants grown under Cd and Pb stress. *International Journal of Advanced Research in Biological Sciences*, 2(6), 1-17
- Alison, M.K. (2006). Guide to common macrolichens and bryophytes of the Umatilla National Forest.
- Alhasnawi, A. (2019). Role of proline in plant stress tolerance: A mini review. *Resurrect Crops*, 20(1), 223-229. <https://doi.org/10.31830/2348-7542.2019.032>
- Ali, S., Fakhri, Y., Golbini, M., Thakur, S.K., Alinejad, A., Parseh, I., Shekhar, S., & Bhattacharya, P. (2019). Concentration of fluoride in groundwater of India: A systematic review, meta-analysis and risk assessment. *Groundwater for Sustainable Development*, 9, <https://doi.org/10.1016/j.gsd.2019.100224>
- Álvarez, R., del Hoyo, A., Díaz-Rodríguez, C., Coello, A.J., del Campo, E.M., Barreno, E., Catalá, M., & Casano, L.M. (2015). Lichen rehydration in heavy metal-polluted environments: Pb modulates the oxidative response of both *Ramalina farinacea* Thalli and its isolated microalgae. *Microbial Ecology*, 69(3), 698–709. <https://doi.org/10.1007/s00248-014-0524-0>
- Amnan, M.A.M., Aizat, W.M., Khaidizar, F.D., & Tan, B.C. (2022). Drought stress induces morpho-physiological and proteome changes of *Pandanus amaryllifolius*. *Plants*, 11, 221. <https://doi.org/10.1101/2021.09.27.461768>
- Amine-Khodja, I.R., Boscari, A., Riah, N., Kechid, M., Maougal, R.T., Belbekri, N., & Djekoun, A. (2022). Impact of two strains of *Rhizobium leguminosarum* on the adaptation to terminal water deficit of two cultivars *Vicia faba*. *Plants*, 11(4), 515. <https://doi.org/10.3390/plants11040515>
- Arif, M.S., Yasmeen, T., Shahzad, S.M., Riaz, M., Rizwan, M., Iqbal, S., Asif, M., Soliman, M.H., & Ali, S. (2019). Lead toxicity induced phytotoxic effects on mung bean can be relegated by lead tolerant *Bacillus subtilis* (PbRB3). *Chemosphere*, 234, 70-80. <https://doi.org/10.1016/j.chemosphere.2019.06.024>
- Armstrong, R.A. (2017). Adaptation of Lichens to Extreme Conditions. In: Shukla V, Kumar S, Kumar N. (eds.). *Plant Adaptation Strategies in Changing Environment*. Springer, Singapore, pp. 1-27. [https://doi.org/10.1007/978-981-10-6744-0\\_1](https://doi.org/10.1007/978-981-10-6744-0_1)
- Ashraf, M., & Harris, P.J.C. (2013). Photosynthesis under stressful environments: An overview. *Photosynthetica*, 51(2), 163-190. <https://doi.org/10.1007/s11099-013-0021-6>
- Bajpai, J. (2013). Fluoride carcinogenesis: The jury is still out!. *South Asian journal of cancer*, 2, 192. <https://doi.org/10.4103/2278-330X.119881>
- Bajpai, R., Semwal, M., & Singh, C.P. (2018). Suitability of lichens to monitor climate change. *Cryptogam Biodiversity and Assessment, Special Volume*, 182-188. <https://doi.org/10.21756/cab.esp13>
- Bajpai, R., Upreti, D.K., Nayaka, S., & Kumari, B. (2010). Biodiversity, bioaccumulation and physiological changes in lichens growing in the vicinity of coal-based thermal power plant of Raebareli district, north India. *Journal of Hazardous Materials*, 174(1-3), 429-436. <https://doi.org/10.1016/j.jhazmat.2009.09.071>
- Balarinová, K., Barták, M., Hazdrová, J., Hájek, J., & Jílková, J. (2014). Changes in photosynthesis, pigment composition and glutathione contents in two Antarctic lichens during a light stress and recovery. *Photosynthetica*, 52(4), 538-547. <https://doi.org/10.1007/s11099-014-0060-7>
- Bamagoos, A.A., Mallhi, Z.I., El-Esawi, M.A., Rizwan, M., Ahmad, A., Hussain, A., Alharby, H.F., Alharbi, B.M., & Ali, S. (2022). Alleviating lead-induced phytotoxicity and enhancing the phytoremediation of castor bean (*Ricinus communis* L.) by glutathione application: new insights into the mechanisms regulating antioxidants, gas exchange and lead uptake. *International Journal of Phytoremediation*, 24(9), 933-944. <https://doi.org/10.1080/15226514.2021.1985959>

- Banerjee, A., & Roychoudhury, A. (2019). Fluorine: a biohazardous agent for plants and phytoremediation strategies for its removal from the environment. *Biologia Plantarum*, 63, 104-112. <https://doi.org/10.32615/bp.2019.013>
- Barbosa, Jr. F., Ramires, I., Rodrigues, M.H.C., Saint' Pierre, T.D., Curtius, A.J., Buzalaf, M.R., Gerlach, R.F., & Tanus-Santos, J.E. (2006). Contrasting effects of age on the plasma/whole lead ratio in men and women with a history of lead exposure. *Environmental Research*, 102, 90-95. <https://doi.org/10.1016/j.envres.2006.03.008>
- Barry, P.S.I. (1981). Concentrations of lead in the tissues of children. *British journal of industrial medicine*, 38, 61-71. <https://doi.org/10.1136/oem.38.1.61>
- Batool, M., Abdullah, S., Umar Ijaz, M., Kousar, S., Tatima, M., Ilyas, R., Ambreen, F., & Mughal, K.T. (2018). heavy metals (Cadmium and Lead) induced oxidative stress in *Channa marulius* and *Wallago attu* during acute toxicity experiments. *Pakistan Journal of Zoology supplement series*, 13, 74-79
- Beckett, R., Minibayeva, F., Solhaug, K., & Roach, T. (2021). Photoprotection in lichens: Adaptations of photobionts to high light. *The Lichenologist*, 53(1), 21-33. <https://doi.org/10.1017/S0024282920000535>
- Belguidoum, A., Lograda, T., & Ramdani, M. (2021). Ability of metal trace elements accumulation by Lichens, *Xanthoria parietina* and *Ramalina farinacea*, in Megres area (Setif, Algeria). *Acta Scientifica Naturalis*, 8(1), 91-108. <https://doi.org/10.2478/asn-2021-0008>
- Benhamada, O., Benhamada, N., & Leghouchi, E. (2022). Polyphenols and antibacterial activity of *Xanthoria parietina* (L.) Th. Fr. methanol extract under lead stress. *Journal of Applied Biological Sciences*, 16(3), 537-552. <https://doi.org/10.5281/zenodo.7114289>
- Benhamada, O., Benhamada, N., & Leghouchi, E. (2023a). Some indicators of damage and responses of *Xanthoria parietina* (L.) Th. Fr. to fluoride and lead induced-stress. *Journal of Applied Biological Sciences*, 17(1), 69-82. <https://doi.org/10.5281/zenodo.7579804>
- Benhamada, O., Benhamada, N., & Leghouchi, E. (2023b). Oxidative stress induced by fluorine in *Xanthoria parietina* (L.) Th. Fr. *International Journal of Secondary Metabolite*, 10(1), 124-136. <https://doi.org/10.21448/ijsm.1136546>
- Benhamada, O., Laib, E., & Benhamada, N., Charef, S., Chennah, M., Chennouf, S., Derbak, H., Leghouchi, E. (2023c). Oxidative stress caused by lead in the lichen *Xanthoria parietina*. *Acta Scientiarum. Biological Sciences*, 45, e63221. <https://doi.org/10.4025/actasciobiols.v45i1.63221>
- Benítez, A., Medina, J., Vásquez, C., Loaiza, T., Luzuriaga, Y., & Calva, J. (2019). Lichens and bromeliads as bioindicators of heavy metal deposition in ecuador. *Lichen Diversity and Biomonitoring*, 11(2), 28. <https://doi.org/10.3390/d11020028>
- Bhatt, S., Deshpande, M., Chaki, S., Patel, N., Pandey, N., & Soni, B. (2011). Chemical synthesis and characterization of lead sulphide (PbS) Nanoparticles. *AIP Conference Proceedings*, 1349. <https://doi.org/10.1063/1.3605844>
- Bhattacharyya, D.S., Deep, P., Singh, S., & Nayak, B. (2016). Lichen secondary metabolites and its biological activity. *American journal of Pharmtech Research*, 6(6), 28-44.
- Boldyrev, M.A. (2018). Lead: properties, history, and applications. *Wiki Journal of Science*, 1(2), 7. <https://doi.org/10.15347/wjs/2018.007>
- Bonvicini, G., Fregni, A., & Palmonari, C. (2006). Fluorine compounds from industrial sources: the case of ceramic industries. In: Tressaud, A. (ed.). *Fluorine and the environment: atmospheric chemistry, emissions, and lithosphere*. France: Elsevier, Amsterdam, pp. 225–249
- Bose, A., Vashistha, K., & O'Loughlin, B.J. (1983). Another cause of lead toxicity. *Pediatrics*, 72(1), 106-108. PMID: 6866579
- Branquinho, C., Brown, D.H., Máguas, C., & Catarino, F. (1997). Lead (Pb) uptake and its effects on membrane integrity and chlorophyll fluorescence in different lichen species.

- Environmental and Experimental Botany*, 37(2–3), 95-105. [https://doi.org/10.1016/S0098-8472\(96\)01038-6](https://doi.org/10.1016/S0098-8472(96)01038-6)
- Büdel, B., & Scheidegger, C. (1995). Thallus morphology and anatomy. In: Nash III, T.H. (ed.), *Lichen biology*. Cambridge University Press, Cambridge, pp. 37–64
- Büdel, B., & Scheidegger, C. (2008). Thallus morphology and anatomy. In: Nash III, T.H., (ed.), *Lichen biology*, Cambridge University Press: Cambridge, UK, pp. 40–68. ISBN 9780521871624
- Buzalaf, M.A.R., & Whitford, G.M. (2011). Fluoride metabolism. *Monographs in Oral Science*, 22, 20-36. <https://doi.org/10.1159/000325107>
- Caggiano, R., Trippetta, S., & Sabia, S. (2015). Assessment of atmospheric trace element concentrations by lichen-bag near an oil/gas pre-treatment plant in the Agri Valley (southern Italy). *Natural Hazards and Earth System Sciences*, 15(2), 325-333. <https://doi.org/10.5194/nhess-15-325-2015>
- Calcott, M.J., Ackerley, D.F., Knight, A., Keyzers, R.A., & Owen, J.G. (2018). Secondary metabolism in the lichen symbiosis. *Chemical Society Reviews*, 47(5), 1730-1760. <https://doi.org/10.1039/c7cs00431a>
- Carreras, H.A., & Pignata, M.L. (2007). Effects of the heavy metals Cu<sup>2+</sup>, Ni<sup>2+</sup>, Pb<sup>2+</sup> and Zn<sup>2+</sup> on some physiological parameters of the *Usnea amblyoclada*. *Journal of Ecotoxicology and Environmental Safety*, 67(1), 59-66. <https://doi.org/10.1016/j.ecoenv.2006.05.005>
- Chae, H.J., Kim, G.J., Deshar, B., Kim, H.J., Shin, M.J., Kwon, H., Youn, U.J., Nam, J.W., Kim, S.H., Choi, H., & Suh, S.S. (2021). Anticancer activity of 2-O-caffeoyl aliphatic acid extracted from the lichen *Usnea barbata* 2017-KL-10. *Molecules*, 26(13), 3937. <https://doi.org/10.3390/molecules26133937>
- Chakrabarti, S., Patrab, P.K., & Santiniketan. (2014). Biochemical and antioxidant responses of paddy (*Oryza sativa* L.) to fluoride stress. *Fluoride*, 48(1), 56-61
- Chappuis, P. (1991). Les oligo-éléments en médecine et en biologie, Ed. Lavoisier
- Chatterjee, N., Sahu, G., Bag, A., Pal, B., & Hazra, G. (2020). Role of fluoride on soil, plant and Human health: A Review on its sources, toxicity and mitigation strategies. *International Journal of Environment and Climate Change*, 10, 77-90. <https://doi.org/10.9734/IJECC/2020/v10i830220>
- Chen, H., Xu, Y., Chen, H., Liu, H., Yu, Q., & Han, L. (2022). Isolation and identification of polyphenols from fresh sweet sorghum stems and their antibacterial mechanism against foodborne pathogens. *Frontiers in Bioengineering and Biotechnology*, 9, 1-15. <https://doi.org/10.3389/fbioe.2021.770726>
- Chetia, J., Gogoi, N., Gogoi, R., & Yasmin, F. (2021). Impact of heavy metals on physiological health of lichens growing in differently polluted areas of central Assam, North East India. *Plant Physiology Reports*, 26, 210–219. <https://doi.org/10.1007/s40502-021-00575-3>
- Chen, T-H., Kaveevivitchai, W., Jacobson, A.J., & Miljanic, O.S. (2015). Adsorption of fluorinated anesthetics within the pores of a molecular crystal. *Chemical Communication*, 51, 14096-14098. <https://doi.org/10.1039/c5cc04885k>
- Choubisa, S.L. (2021). Toxic effects of fluoride on human bones. *Advances in Pharmacology and Toxicology*, 13(1), 9–13
- Choudhary, S., Rani, M., Devika, O.S., Patra, A., Singh, R.K., & Prasad, S.K. (2019). Impact of fluoride on agriculture: A review on its sources, toxicity in plants and mitigation strategies. *International Journal of Chemical Studies*, 7(2), 1675-1680.
- Chowaniec, K., & Rola, K. (2022). Evaluation of the importance of ionic and osmotic components of salt stress on the photosynthetic efficiency of epiphytic lichens. *Physiology and Molecular Biology of Plants*, 28, 107–121. <https://doi.org/10.1007/s12298-022-01134-2>
- Conti, M.E., & Cecchetti, G.B. (2001) Biological monitoring: Lichens as bioindicators of air pollution assessment-A review. *Environmental Pollution*, 114, 471-492. [http://dx.doi.org/10.1016/S0269-7491\(00\)00224-4](http://dx.doi.org/10.1016/S0269-7491(00)00224-4)

- Conti, M.E., & Tudino, M. (2016). Lichens as biomonitors of heavy metals pollution in book: Comprehensive Analytical Chemistry Volume 73 The Quality of Air. Edition: 1<sup>st</sup> Ed. Chapter: 6, Elsevier. <https://doi.org/10.1016/bs.coac.2016.02.005>
- Crawford, S.D. (2015). Lichens used in traditional medicine. In: Ranković B. (ed.). Lichen secondary metabolites. Springer, Cham, pp. 27–80. [https://doi.org/10.1007/978-3-319-13374-4\\_2](https://doi.org/10.1007/978-3-319-13374-4_2)
- Crompton, T.R. (2000). Battery reference book. Oxford, England: Newnes. 18/2–18/4.
- Cruise, A., Singh, A., & Quiney, R. (2010). Sodium fluoride in otosclerosis treatment: Review. *The Journal of laryngology and otology*, 124(6). 583-586. <http://doi.org/10.1017/S0022215110000241>
- Darnajoux, R., Lutzoni, F., Miadlikowska, J., & Bellenger, J.P. (2015). Determination of elemental baseline using peltigeralean lichens from Northeastern Canada (Québec): Initial data collection for long term monitoring of the impact of global climate change on boreal and subarctic area in Canada. *Science of the Total Environment*, 533, 1-7. <https://doi.org/10.1016/j.scitotenv.2015.06.030>
- Demková, L., Bobul'ská, L., Árvay, J., Jezný, T., & Dučay, L. (2017). Biomonitoring of heavy metals contamination by mosses and lichens around Slovinky tailing pond (Slovakia). *Journal of Environmental Science and Health, Part A, Toxic/Hazardous Substances and Environmental Engineering*, 52(1), 30-36. <https://doi.org/10.1080/10934529.2016.1221220>
- Dennerlein, K., Kiesewetter, F., Kilo, S., Jäger, T., Göen, T., Korinth, G., & Drexler, H (2016). Dermal absorption and skin damage following hydrofluoric acid exposure in an ex vivo human skin model. *Toxicology Letters*, 248, 25-33. <https://doi.org/10.1016/j.toxlet.2016.02.015>
- Deruelle, S., & Lallement, R. (1983). Les lichens témoins de la pollution. Thèmes vuibert Université biologie. (Paris), pp. 48-88
- Dévéhat, F., Thüs, H., Abasq, M.L., Delmail, D., & Boustie, J. (2014). Oxidative stress regulation in lichens and its relevance for survival in coastal habitats. *Advances in Botanical Research*, 71, 467-503. <https://doi.org/10.1016/B978-0-12-408062-1.00016-0>
- Douibi, C., Ramdani, M., Khelfi, A., Benharket, R., Lograda, T., & Chalard, P. (2015). Biomonitoring of heavy metals by lichens in Setif Area (East of Algeria). *Unified Journal of Environmental Science and Toxicology*, 1(1), 001- 013
- Dzubaj, A., Backor, M., Tomko, J., Péli, E., & Tuba, Z. (2008). Tolerance of the lichen *Xanthoria parietina* (L.) Th. Fr. to metal stress. *Ecotoxicology and Environmental Safety*, 70(2), 319-26. <https://doi.org/10.1016/j.ecoenv>
- EFSA, (2013). Panel on dietetic products, nutrition; scientific opinion on dietary reference values for fluoride. *EFSA J.*, 11(8), 3332
- Ekstrand, J. (1996). Fluoride metabolism. In: Fejerskov, O., Ekstrand, J. and Burt, B. (eds.), Fluoride in dentistry, (2<sup>nd</sup> Ed). Munksgaard, Denmark, pp. 55-65
- Eldridge, D.J., & Delgado-Baquerizo, M. (2018). The influence of climatic legacies on the distribution of dryland biocrust communities. *Global Change Biology*, 25(1), 327–336. <https://doi.org/10.1111/gcb.14506>
- Elix, J., & Stocker-Wörgötter, E. (2008). Biochemistry and secondary metabolites. In T.H., Nash III (Ed.), Lichen Biology (pp. 104-133). Cambridge: Cambridge University Press. <https://doi.org/10.1017/CBO9780511790478.008>
- Elkhateeb, W., Elnahas, M., & Daba, G. (2021). Lichentherapy: Highlights on the pharmaceutical potentials of lichens. *Open Access Journal of Microbiology & Biotechnology*, 6(1),1-10. <https://doi.org/10.23880/oajmb-16000190>
- Elkhateeb, W., Elghwas, D., & Daba, G. (2022). Lichens Uses: Surprising uses of lichens that improve Human life. *Journal of Biomedical Research & Environmental Sciences*, 3, 189-194. <https://doi.org/10.37871/jbres1420>

- Eloumi, N., Zouari, M., Mezghani, I., Ben Abdallah, F. Woodward, S., & Kallel, M. (2017). Adaptive biochemical and physiological responses of *Eriobotrya japonica* to fluoride air pollution. *Ecotoxicology*, 26, 991–1001. <https://doi.org/10.1007/s10646-017-1827-y>
- Esposito, S., Sorbo, S., Conte, B., & Basile, A. (2012). Effects of heavy metals on ultrastructure and HSP70S induction in the aquatic moss *Leptodictyum Riparium* Hedw. *International Journal of Phytoremediation*, 14(4), 443-455. <https://doi.org/10.1080/15226514.2011.620904>
- Expósito, J.R., Barreno, E., & Catalá, M. (2022). 18 - Role of NO in lichens. In: Singh V.P., Singh S., Tripathi D.K., Romero-Puertas M.C. and Sandalio M.L. (eds), Nitric Oxide in Plant Biology. *Academic Press*, pp. 407-429. <https://doi.org/10.1016/B978-0-12-818797-5.00027-3>
- Expósito, J.R., Barreno, E., & Catalá, M. (2019). Biological strategies of lichen symbionts to the toxicity of lead (Pb). In book: Lead in plants and the environment, pp.149-170. [https://doi.org/10.1007/978-3-030-21638-2\\_9](https://doi.org/10.1007/978-3-030-21638-2_9)
- Fawell, J., Bailey, K., Chilton, J., Dahi, E., Fewtrell, L., & Magara, Y. (2006), Fluoride in drinking-water. London: World Health Organization (WHO). [Access: March 16 2015]. <http://apps.who.int/iris/bitstream/10665/43514/1/9241563192>
- Filella, M., & Bonet, J. (2017). Environmental impact of alkyl lead (IV) Derivatives: Perspective after their Phase-out. *Metal Ions in Life Sciences*, 10, 17. <https://doi.org/10.1515/9783110434330-014>
- Filler, R., & Saha, R. (2009). Fluorine in medicinal chemistry: a century of progress and a 60-year retrospective of selected highlights. *Future Medicinal Chemistry*, 1(5), 777-791. <http://doi.org/10.4155/fmc.09.65>
- Fordyce, F. (2011). Fluorine: Human Health Risks. *Encyclopedia of Environmental Health*, 2, 776-785. <https://doi.org/10.1016/B978-0-444-52272-6.00697-8>
- Fuge, R. (2018). Fluorine in the environment, a review of its sources and geochemistry. *Applied Geochemistry*, 100, 393-406. <https://doi.org/10.1016/J.APGEOCHEM.2018.12.016>
- Gad, S.C., & Pham, T. (2014). Lead. *Encyclopedia of Toxicology* (3<sup>rd</sup> Ed.), pp. 61-65. <https://doi.org/10.1016/B978-0-12-386454-3.00868-X>
- Gandhi, A.D., Umamahesh, K., Sathiyaraj, S., Suriyakala, G., Velmurugan, R., Al Farraj, D.A., Gawwad, M.R.A., Murugan, K., Babujanathanam, R., & Saranya, R. (2022). Isolation of bioactive compounds from lichen *Parmelia sulcata* and evaluation of antimicrobial property. *Journal of Infection and Public Health*, 15(4), 491-497. <https://doi.org/10.1016/j.jiph.2021.10.014>
- Gangola, M.P., & Ramadoss, B.R. (2018). Chapter 2 - Sugars play a critical role in abiotic stress tolerance in plants. In: Wani S.H. (ed.), Biochemical, physiological and molecular avenues for combating abiotic stress tolerance in plants, Edition: (1<sup>st</sup> Ed.) *Academic Press*, pp. 17-38. <https://doi.org/10.1016/B978-0-12-813066-7.00002-4>
- Garty, J., Leher, H., Garty-spitz, R.L., Ganor, E., Stupp, A., Alpert, P., & Osetinsky, I. (2008). Temporal fluctuations of mineral concentrations as related to the physiological status of the lichen *Ramalina lacera* (With.) J.R. Laund. *Israel Journal of Plant Sciences*, 56(4), 361-369. <https://doi.org/10.1560/IJPS.56.4.361>
- Gauslaa, Y., Mikulec, M.M., & Solhaug, K.A. (2021). Short-term growth experiments – A tool for quantifying lichen fitness across different mineral settings. *Flora - Morphology Distribution Functional Ecology of Plants*, 282(3), 151900. <https://doi.org/10.1016/j.flora.2021.151900>
- Gessner, D.K., Ringseis, R., & Eder, K. (2017). Potential of plant polyphenols to combat oxidative stress and inflammatory processes in farm animals. *Journal of Animal Physiology and Animal Nutrition*, 101(4), 605-628. <https://doi.org/10.1111/jpn.12579>
- Ghazi, A.M., & Millette, J.R. (1964). 4 – Lead. *Environmental Forensics*, 55-79. <https://doi.org/10.1016/B978-012507751-4/50026-4>

- Ghosh, U.K., Islam, M.N., Siddiqui, M.N., Cao, X., & Khan, M.A.R. (2022). Proline, a multifaceted signalling molecule in plant responses to abiotic stress: understanding the physiological mechanisms. *Plant Biology*, 24(2), 227-239. <https://doi.org/10.1111/plb.13363>
- Gilbert, O.L. (1973). The effect of airborne fluorides, in: Ferry, B.W., Baddeley, M.S and Hawksworth D.L (Eds), *Air Pollution and Lichens*. Athlone, London, p 176
- Goncharov, N., Savelieva, E., Koryagina, N., Zinchenko, V., Kuznetsov, S., Mindukshev, I., Avdonin, P., Ukolov, A., & Jenkins, R. (2020). Fluoroacetate. In: Gupta R.C. (ed.), *Handbook of Toxicology of Chemical Warfare Agents* (3<sup>rd</sup> Ed.), Academic Press, pp. 215-238, ISBN 9780128190906, <https://doi.org/10.1016/B978-0-12-819090-6.00015-5>
- Gong, B., Sun, S., Yan, Y., Jing, X., & Shi, Q. (2018). Glutathione metabolism and its function in higher plants adapting to stress. In: Gupta, D., Palma, J., Corpas, F. (eds) *Antioxidants and antioxidant enzymes in higher plants*. Springer, Berlin, 181-205. [https://doi.org/10.1007/978-3-319-75088-0\\_9](https://doi.org/10.1007/978-3-319-75088-0_9)
- Gurbanov, R., & Unal, D. (2019) The biomolecular alterations in *Cladonia convoluta* in response to lead exposure. *Spectroscopy Letters*, 51, 563-570. <https://doi.org/10.1080/00387010.2018.1533564>
- Gupta, S.P. (2019). Roles of fluorine in drug design and drug action. *Letters in Drug Design & Discovery*, 16(10), 1089 – 1109. <http://doi.org/10.2174/1570180816666190130154726>
- Guth, S., Hüser, S., Roth, A., Degen, G., Diel, P., Edlund, K., ... Hengstler, J.G. (2020). Toxicity of fluoride: critical evaluation of evidence for human developmental neurotoxicity in epidemiological studies, animal experiments and in vitro analyses. *Archives of Toxicology*, 94(5), 1375-1415. <https://doi.org/10.1007/s00204-020-02725-2>
- Hasanuzzaman, M., Bhuyan, M.H.M.B., Parvin, K., Bhuiyan, T.F., Anee, T.I., Nahar, K., Hossen, M.S., Zulfiqar, F., Alam, M.M., & Fujita, M. (2020). Regulation of ROS metabolism in plants under environmental stress: A Review of Recent Experimental Evidence. *International Journal of Molecular Sciences*, 21(22), 8695. <https://doi.org/10.3390/ijms21228695>
- Hauck, M., Willenbruch, K., & Leuschner, C. (2009). Lichen substances prevent lichens from nutrient deficiency. *Journal of Chemical Ecology*, 35, 71-73. <https://doi.org/10.1007/s10886-008-9584-2>
- Hernberg, S. (2000). Lead poisoning in a historical perspective. *Journal of Intensive Medicine*, 38(3), 244-54. [https://doi.org/10.1002/1097-0274\(200009\)38\(3\), 244-54. https://doi.org/10.1002/1097-0274\(200009\)38\(3\), 244-54.](https://doi.org/10.1002/1097-0274(200009)38(3)<244::AID-JIMB244>3.0.CO;2-3)
- Honegger, R. (1998). The Lichen Symbiosis - What is so spectacular about it? *The Lichenologist*, 30(3), 193-212
- Ingram, G.S., Agalamanyi, E.A., & Higham, S.M. (2005). Caries and fluoride processes. *Journal of Dentistry*, 33(3), 187-191. <https://doi.org/10.1016/j.jdent.2004.10.004>
- Ite, A.E., Udousoro, I.I., & Ibok, U.J. (2014). Distribution of some atmospheric heavy metals in lichen and moss samples collected from Eket and Ibeno local government areas of Akwa Ibom State, Nigeria. *American Journal of Environmental Protection*, 2(1), 22-31. <https://doi.org/10.12691/env-2-1-5>
- James, A.C., Stahlhofen, W., Rudolf, G., Köbrich, R., Briant, J.K., Egan, M.J., Nixon, W., & Birchall, A. (1994). Deposition of inhaled particles. *Annals of ICRP* 24(1-3), 231-299. [https://doi.org/10.1016/0146-6453\(94\)90042-6](https://doi.org/10.1016/0146-6453(94)90042-6)
- Kabir, M., Habiba, U., Iqbal, M., Shafiq, M., & Farooqi, Z. (2020). Industrial pollution and its impacts on ecosystem: A Review. *Biochemical Research*, 17(2), 1364-1372
- Kamel, H.A. (2008). Lead accumulation and its effect on photosynthesis and free amino acids in *Vicia faba* grown hydroponically. *Australian Journal of Basic and Applied Sciences*, 2(3), 438-446
- Kandelinskaya, O., Grischenko, H., Hihinyak, Y., Andreev, M., Convey, P., Lukashanets, D., Kozel, N., & Prokopiev, I. (2021). Chemical compounds and antioxidant activity of

- Antarctic lichens. *Antarctic Science*, 34(1), 3-15. <https://doi.org/10.1017/S0954102021000511>
- Kapusta, P., & Sobczyk, Ł. (2015). Effects of heavy metal pollution from mining and smelting on enchytraeid communities under different land management and soil conditions. *Science of the Total Environment*, 1, 536, 517-526. <https://doi.org/10.1016/j.scitotenv.2015.07.086>
- Karakoti, N., Bajpai, R., Upreti, D.K., Mishra, G.K., Srivastava, A., & Nayaka, S. (2014). Effect of metal content on chlorophyll fluorescence and chlorophyll degradation in lichen *Pyxine cocus* (Sw.) Nyl.: a case study from Uttar Pradesh, India. *Environmental Earth Sciences*, 71(5). <https://doi.org/10.1007/s12665-013-2623-5>
- Khan, M., Al Azzawi, T.N.I., Imran, M., Hussain, A., Mun, B.G., Pande, A., & Yun, B.W. (2021). Effects of lead (Pb)-induced oxidative stress on morphological and physio-biochemical properties of rice. *Biocell*, 45(5), 1413-1423. <https://doi.org/10.32604/biocell.2021.015954>
- Khan, N., Ali, S., Zandi, P., Mehmood, A., Ullah, S., Ikram, M., Ismail, I., Shahid, M., & Babar, Md. (2020). Role of sugars, amino acids and organic acids in improving plant abiotic stress tolerance. *Pakistan Journal of Botany*, 52(2). [https://doi.org/10.30848/PJB2020-2\(24\)](https://doi.org/10.30848/PJB2020-2(24))
- Kiani, R., Arzani, A., & Maibody, S.A.M. (2021). Polyphenols, flavonoids, and antioxidant activity involved in salt tolerance in wheat, *Aegilops cylindrica* and their amphidiploids. *Frontiers in Plant Science*, 12, 646221. <https://doi.org/10.3389/fpls.2021.646221>
- Kim, II-S., Song, W., & Arakawa, H. (2019). The role of low-level sodium fluoride in periodontal inflammation. *Journal of Hard Tissue Biology*, 28(2), 159-164. <http://doi.org/10.2485/jhtb.28.159>
- Kim, A.K., & Su, J.Z. (1999). Full-scale evaluation of halon replacement agents. *Journal of Fire Protection Engineering*, 10(2), 1-23. <https://doi.org/10.1177/104239159901000201>
- Kleerekoper, M. (1998). The role of fluoride in the prevention of osteoporosis. *Endocrinology and Metabolism Clinics of North America*, 27(2), 441-52. [http://doi.org/10.1016/s0889-8529\(05\)70015-3](http://doi.org/10.1016/s0889-8529(05)70015-3)
- Koch, N.M., Matos, P., Branquinho, C., Pinho, P., Lucheta, F., de Azevedo Martins, S.M., & Ferrao Vargas, V.M. (2019). Selecting lichen functional traits as ecological indicators of the effects of urban environment. *Science of the Total Environment*, 654, 705–713. <https://doi.org/10.1016/j.scitotenv>
- Kołton, A., Długosz-Grochowska, O., Wojciechowska, R., & Czaja, M. (2022). Biosynthesis regulation of folates and phenols in plants. *Scientia Horticulturae*, 291, 110561. <https://doi.org/10.1016/j.scienta.2021.110561>
- Kováčik, J., Dresler, S., Peterková, V., & Babula, P. (2018). Metal-induced oxidative stress in terrestrial macrolichens. *Chemosphere*, 203, 402-409. <https://doi.org/10.1016/j.chemosphere.2018.03.112>
- Kováčik, J., Rotková, G., Bujdoš, M., Babula, P., Peterková, V., & Matuš, P. (2017). Ascorbic acid protects *Coccomyxa subellipsoidea* against metal toxicity through modulation of ROS/NO balance and metal uptake. *Journal of Hazardous Materials*, 339, 200–207. <https://doi.org/10.1016/j.jhazmat.2017.06.035>
- Kraft, M., Scheidegger, C., & Werth, S. (2022). Stressed out: the effects of heat stress and parasitism on gene expression of the lichen-forming fungus *Lobaria pulmonaria*. *The Lichenologist*, 54, 71-83. <https://doi.org/10.1017/S0024282921000463>
- Kranner, I., Beckett, R., Hochman, A., & Nash III, T.H. (2009). Desiccation-tolerance in lichens: A Review. *The Bryologist*, 111, 576-593. <https://doi.org/10.1639/0007-2745-111.4.576>
- Kuang, P., Deng, H., Cui, H., Chen, L., Fang, J., Zuo, Z., Deng, J., Wang, X., & Zhao, L. (2016). Sodium fluoride (NaF) causes toxic effects on splenic development in mice. *Oncotarget*, 8, 4703-4717, <https://doi.org/10.18632/oncotarget.13971>

- Kularatne, K.I.A., & de Freitas C.R. (2013). Epiphytic lichens as biomonitors of airborne heavy metal pollution. *Environmental and Experimental Botany*, 88, 24-32. <https://doi.org/10.1016/j.envexpbot.2012.02.010>
- Kuldeep, S., & Prodyut, B. (2015). Lichen as a bio-indicator tool for assessment of climate and air pollution vulnerability: Review. *International Research Journal of Environment Sciences*, 4(12), 107-117
- LeBlanc, F., Comeau, G., & Rao, D.N. (2011). Fluoride injury symptoms in epiphytic lichens and mosses. *Canadian Journal of Botany*, 49(9), 1691-1698. <https://doi.org/10.1139/b71-238>
- Lee, Y.J., & Jeong, I.B. (2021). Chemical pneumonitis by prolonged hydrogen fluoride inhalation. *Respiratory Medicine Case Reports*, 32, 101338. <https://doi.org/10.1016/j.rmcr.2020.101338>
- Lei, S., Rossi, S., & Huang, B. (2022). Metabolic and physiological regulation of aspartic acid-mediated enhancement of heat stress tolerance in *Perennial Ryegrass*. *Plants*, 11, 199. <https://doi.org/10.3390/plants11020199>
- Li, X., Liu, J., Li, X., Liu, H., Liu, H., Li, Y., Liu, Y., & Dong, Y. (2018). Recent advance in the synthesis of (1,1-difluoroethyl) arenes. *Journal of Fluorine Chemistry*, 216, 102-106. <https://doi.org/10.1016/j.jfluchem.2018.10.011>
- Liang, X., Zhang, L., Natarajan, S.K., & Becker, D.F. (2013). Proline mechanisms of stress survival. *Antioxidants and Redox Signaling*, 19(9). <https://doi.org/10.1089/ars.2012.5074>
- Lin, S., Wang, X., Yu, I.T., Tang, W., Miao, J., Li, J., Wu, S., & Lin, X. (2011). Environmental lead pollution and elevated blood lead levels among children in a rural area of China. *American Journal of Public Health*, 101(5), 834-841. <https://doi.org/10.2105/AJPH.2010.193656>
- Lu, F.C. (1992). Basic toxicology: fundamentals, target organs, and risk assessment. - Hemisphere publishing corporation, Ed. Masson, p. 303, 304
- Maciąg, D.M., Węgrzyn, G., & Guzow, K.B. (2014). Antibacterial activity of lichen secondary metabolite usnic acid is primarily caused by inhibition of RNA and DNA synthesis. *FEMS Microbiology Letters*, 353(1), 57-62. <https://doi.org/10.1111/1574-6968.12409>
- Marques, J., Gonçalves, J., Oliveira, C., Favero-Longo, S.E., Paz-Bermúdez, G., Almeida, R., & Prieto, B. (2016). On the dual nature of lichen-induced rock surface weathering in contrasting micro-environments. *Ecology*, 97(10), 2844-2857. <https://doi.org/10.1002/ecy.1525>
- Matos, P., Pinho, P., Aragon, G., Martínez, I., Nunes, A., Soares, A.M.V.M., & Branquinho, C. (2015). Lichen traits responding to aridity. *Journal of Ecology*, 103(2), 451-458. <https://doi.org/10.1111/1365-2745.12364>
- Mishra, A., Ishwakarma, K., Malaviya, P., Kumar, N., Pavón, L.R., Shandilya, C., Sharma, R., Bisht, A., & Takkar, S. (2022). On plant epigenomes for food security. In: Thakur, I.S., Ngo, H.H, Socol, C.R., and Larroche, C. (Eds), Ashok Pandey Influence of greenhouse gases. Biomass, Biofuels, Biochemicals, Elsevier, pp. 421-450, ISBN 9780128235003. <https://doi.org/10.1016/B978-0-12-823500-3.00003-0>
- Mikheeva, E., Prosekov, A., & Volobaev, V. (2020). Genotoxic properties of fluorine (review). *Hygiene and Sanitation*, 99(3), 253-258. <https://doi.org/10.33029/0016-9900-2020-99-3-253-258>
- Mitrović, T., Stamenkovic, S., Cvetković, V., Nikolic, M., Tošić, S., & Stojičić, D. (2011). Lichens as source of versatile bioactive compounds. *Biologica Nyssana*, 2(1), 1-6
- Mohideen, H., Dahiya, D.S., Parsons, D., Hussain, H., & Syed Ahmed, R. (2022). Skeletal fluorosis: A case of inhalant abuse leading to a diagnosis of colon cancer. *Journal of Investigative Medicine High Impact Case Reports*, 10, 1-6. <https://doi.org/10.1177/23247096221084919>
- Moissan, H. (1886). Le Fluor. *La Nature*, 701, 363-366



- Mondal, N.K. (2017). Effect of fluoride on photosynthesis, growth and accumulation of four widely cultivated rice (*Oryza sativa* L.) varieties in India. *Ecotoxicology and Environmental Safety*, 144, 36-44. <https://doi.org/10.1016/j.ecoenv.2017.06.009>
- Mohamed, E., Mohamed, L., & Abdelhay, E.G. (2020). Using calcicolous and corticolous lichens to assess lead and cadmium air pollution of the Moroccan Atlantic Coast Safi-Essaouira. *Polish Journal of Environmental Studies*, 29(1), 779-787. <https://doi.org/10.15244/pjoes/102629>
- Morillas, L., Roales, J., Cruz, C., & Munzi, S. (2022). Lichen as multipartner symbiotic relationships. *Encyclopedia*, 2, 1421–1431. <https://doi.org/10.3390/encyclopedia2030096>
- Mukemre, M., Zengin, G., Turker, R.S., Aslan, A., & Dalar, A. (2021). Biological activities and chemical composition of *Xanthoria* lichens from Turkey. *International Journal of Secondary Metabolite*, 8(4), 376–388. <https://doi.org/10.21448/ijsm.994427>
- Mundada, P.S., Jadhav, S.V., Salunkhe, S.S., Gurme, S.T., Umdale, S.D., Nikam, T.D., & Ahire, M.L. (2021). Plant performance and defensive role of proline under environmental stress. In: Husen A. (ed.), *Plant Performance Under Environmental Stress*. Springer; Berlin/Heidelberg, pp. 201-223. [https://doi.org/10.1007/978-3-030-78521-5\\_8](https://doi.org/10.1007/978-3-030-78521-5_8)
- Nahar, K., Hasanuzzaman, M., Suzuki, T., & Fujita, M. (2017). Polyamines-induced aluminum tolerance in mung bean: A study on antioxidant defense and methylglyoxal detoxification systems. *Ecotoxicology*, 26(1), 58-73. <https://doi.org/10.1007/s10646-016-1740-9>
- Nareshkumar, A., Veeranagamallaiah, G., Pandurangaiah, M., Kiranmai, K., Amaranathareddy, V., Lokesh, U., Venkatesh, B., & Sudhakar, C. (2015). Pb-stress induced oxidative stress caused alterations in antioxidant efficacy in two groundnut (*Arachis hypogaea* L.) Cultivars. *Agricultural Sciences*, 6(10), 1283-1297. <https://doi.org/10.4236/as.2015.610123>
- Nash III, T.H. (1971). Lichen sensitivity to hydrogen fluoride. *Bulletin of the Torrey Botanical Club*, 98(2), 103-106
- Nayaka, S., & Haridas, B. (2020). Bioactive secondary metabolites from lichens. In book: *Plant metabolites: Methods, applications and prospects* (pp.255-290), Publisher: Springer, Singapore. [https://doi.org/10.1007/978-981-15-5136-9\\_12](https://doi.org/10.1007/978-981-15-5136-9_12)
- Nielsen, E. (2013). Lead and inorganic lead compounds. Evaluation of health hazards and estimation of a quality criterion in soil. *The Danish Environmental Protection Agency, Strandgade*, 29, 1401 Copenhagen K, Denmark, [www.mst.dk/english](http://www.mst.dk/english). ISBN: 978-87-93026-73-5
- Nobile, V., Schiano, I., Peral, A., Giardina, S., Spartà, E., & Caturla, N. (2021). Antioxidant and reduced skin-ageing effects of a polyphenol-enriched dietary supplement in response to air pollution: a randomized, double-blind, placebo-controlled study. *Food and Nutrition Research*, 65. <https://doi.org/10.29219/fnr.v65.5619>
- Norman, H.O., & Arden, C.G. (1991). *Water fluoridation in primary preventive dentistry*. (3<sup>rd</sup> Ed.). Stamford, CT: Appleton and Lange
- Nimis, P.L., Aptroot, A., Boonpragob, K., Buaruang, K., Poengsungnoen, V., Polyiam, W., Vongshewarat, K., Meesim, S., Boonpeng, C., Phokaeo, S., Molsil, M., Nirongbutr, P., Sangvichien, E., Moro, A., Pittao, E., & Martellos, S. (2017). 100 Lichens from Thailand: a tutorial for students (online) ISBN 978-88-8303-853-2 EUT - *Edizioni Università di Trieste Via E. Weiss*, 21, 34128 Trieste <https://eut.units.it>
- Nugraha, A.S., Pratoko, D.K., Damayanti, Y.D., Lestari, N.D., Laksono, T.A., Addy, H.S., Untari, L.F., Kusumawardani, B., & Wangchuk, P. (2019). Antibacterial and anticancer activities of nine lichens of Indonesian Java Island. *Journal of Biologically Active Products from Nature*, 9(1), 39-46. <https://doi.org/10.1080/22311866.2019.1567383>
- Ozenda, P. (2000). *Les végétaux, organisation et diversité biologique*, Ed. Masson (2<sup>nd</sup> Ed.), 192p
- Ozenda, P., & Clauzade, G. (1970). *Les Lichens: Étude biologique et flore illustrée*. Paris, Ed. Masson (2<sup>nd</sup> Ed.), pp. 633-634

- Pak, C., Zerwekh, J., Antich, P., Bell, N., & Singer, F. (2009). Slow-release sodium fluoride in osteoporosis. *Journal of Bone and Mineral Research*, 11(5), 561-564. <http://doi.org/10.1002/jbmr.5650110502>
- Paoli, L., Munzi, S., Guttova, A., Senko, D., Sardella, G., & Loppi, S. (2015). Lichens as suitable indicators of the biological effects of atmospheric pollutants around a municipal solid waste incinerator (S Italy). *Ecological Indicators*, 52. <https://doi.org/10.1016/j.ecolin.d.2014.12.018>
- Papanikolaou, N.C., Hatzidaki, E.G., Belivanis, S., Tzanakakis, G.N., & Tsatsakis, A.M. (2005). Lead toxicity update. A brief review. *Medical Science Monitor*, 11(10), 329-336. PMID: 16192916
- Pavlov, D. (2017). Lead-acid batteries: science and technology (2<sup>nd</sup> Ed.), pp. 245-273. <https://doi.org/10.1016/B978-0-444-59552-2.00005-5>
- Pelc, J., Śnioszek, M., Wróbel, J., & Telesiński, A. (2020). Effect of fluoride on germination, early growth and antioxidant enzymes activity of three winter wheat (*Triticum aestivum* L.) cultivars. *Applied Sciences*, 10(19). <https://doi.org/10.3390/app10196971>
- Perkins, D.F. (1992). Relationship between fluoride contents and loss of lichens near an aluminium works. *Water Air and Soil Pollution*, 64, 503-510. <https://doi.org/10.1007/BF00483360>
- Perlmutter, G.B. (2009). Basic Lichenology 2: Reproduction. *Bulletin of the California Lichen Society*, 16(1), 7-11
- Pescott, O.L., Simkin, J.M., August, T.A., Randle, Z., Dore, A.J., & Botham, M.S. (2015). Air pollution and its effects on lichens, bryophytes, and lichens-feeding *Lepidoptera*: review and evidence from biological records. *Biological Journal of the Linnean Society*, 115(3), 611-635. <https://doi.org/10.1111/bij.12541>
- Philip, A.T., & Gerson, B. (1994). Lead poisoning-Part I. incidence, etiology, and toxicokinetic. *Clinical and Laboratory Medicine*, 14(2), 423-444. PMID: 7924196
- Pisani, T., Munzi, S., Paoli, L., Bac'kor, M., & Loppi, S. (2009). Physiological effects of a geothermal element: Boron excess in the epiphytic lichen *Xanthoria parietina* (L.) TH. FR. *Chemosphere*, 76(7), 921-926. <https://doi.org/10.1016/j.chemosphere.2009.04.058>
- Podterob, A.P. (2008). Chemical composition of lichens and their medical applications. *Pharmaceutical Chemistry Journal*, 42, 582-588. <https://doi.org/10.1007/s11094-009-0183-5>
- Pollick, H. (2018). The role of fluoride in the prevention of tooth decay. *Pediatric clinics of North America*, 65(5), 923-940. <https://doi.org/10.1016/j.pcl.2018.05.014>
- Popescu, M., Blanchard, J-M., & Carre, J. (1998). Analyse et traitement physicochimique des rejets atmosphériques industriels (émissions, fumées, odeurs & poussières). Ed. Lavoisier, 854 p.
- Purvis, O.W. (2014). Adaptation and interaction of saxicolous crustose lichens with metals. *Botanical Studies*, 55(1), 23. <https://doi.org/10.1186/1999-3110-55-23>
- Quijano-Abril, M.A., Ramirez-Ospina, D.M., Domínguez-Rave, M.I., & Londoño-Valencia, J. (2021). Lichens as biosensors for the evaluation of urban and sub-urban air pollution in a tropical mountain valley, Rionegro, Antioquia. *Revista Bionatura*, 6(1), 1501-1509. <https://doi.org/10.21931/RB/2021.06.01.10>
- Ram, A., Verma, P., & Gadi, B.R. (2014). Effect of fluoride and salicylic acid on seedlings growth and biochemical parameters of watermelon (*Citrullus lanatus*). *Research report Fluoride*, 47(1), 49-55
- Ribeiro, D., Yujra, V., Hugo, V., Claudio, S., Estadella, D., Viana, M., & Oshima, C. (2017). Putative mechanisms of genotoxicity induced by fluoride: a comprehensive review. *Environmental Science and Pollution Research*, 24(2). <https://doi.org/10.1007/s11356-017-9105-3>

- Roberts, B., & Thompson, L.K., (2011). Lichens as indicators of fluoride emission from a phosphorus plant, Long Harbour, Newfoundland, Canada. *Canadian Journal of Botany*, 58(20), 2218-2228. <https://doi.org/10.1139/b80-256>
- Rodríguez, E.M., Marante, F.G.T., Hernández, J.C., Barrera, J.B., & Rosa, F.J.E. (2016). Antioxidant activity of polyphenols from *Hypogymnia tavaresii* D. Hawksw & P. James. *Quimica Nova*, 39(4), 456-461. <https://doi.org/10.5935/0100-4042.20160053>
- Rola, K. (2020). Insight into the pattern of heavy-metal accumulation in lichen thalli. *Journal of Trace Elements in Medicine and Biology*, 61, 126512. <https://doi.org/10.1016/j.jtemb.2020.126512>
- Rola, K., Latkowska, E., Myśliwa-Kurdziel, B., & Osyczka, P. (2019). Heavy-metal tolerance of photobiont in pioneer lichens inhabiting heavily polluted sites. *Science of the Total Environment*, 279, 260-269. <https://doi.org/10.1016/j.scitotenv.2019.05.002>
- Sakai, T. (2000). Biomarkers of lead exposure. *Industrial Health*, 38(2), 127-142. <http://dx.doi.org/10.2486/indhealth.38.127>
- Sahariya, A., Bharadwaj, C., Iwuala, E., & Alam, A. (2021). Fluoride toxicity in soil and plants: an overview. 8, 26-34
- Sanità di Toppi, L., Pawlik-Skowrońska, B., Vurro, E., Vattuone, Z., Kalinowska, R. Restivo, F.M., Musetti, R., & Skowroński, T. (2008). First and second line mechanisms of cadmium detoxification in the lichen photobiont *Trebouxia impressa* (Chlorophyta). *Environmental Pollution*, 151(2), 280-286.: <https://doi.org/10.1016/j.envpol.2007.06.010>
- Sargsyan, R., Gasparyan, A., Tadevosyan, G., & Panosyan, H. (2021). Antimicrobial and antioxidant potentials of non-cytotoxic extracts of corticolous lichens sampled in Armenia. *AMB Express*, 11(1), 110. <https://doi.org/10.1186/s13568-021-01271-z>
- Schaefer, L., & Fegley, B. (2005). Silicon tetrafluoride on Io. *Icarus*, 179, 252–258. <https://doi.org/10.1016/j.icarus.2005.05.020>
- Šeklić, D.S., Jovanović, M.M, Virijević, K.D., Grujić, J.N, Živanović, M.N., & Marković, S.D. (2022). *Pseudevernia furfuracea* inhibits migration and invasion of colorectal carcinoma cell lines. *Journal of Ethnopharmacology*, 287(10), 114758, <https://doi.org/10.1016/j.jep.2021.114758>
- Semadi, A. (1989). Effets de la pollution atmosphérique (pollution globale, fluorée et plombique) sur la végétation dans la région de Annaba (Algérie). Thèse de Doctorat, France. Corpus ID: 128261548. ISSN 0294-1767
- Sharma, P., & Dubey, R. (2005). Lead toxicity in plants. *Brazilian Journal of Plant Physiology*, 17(1), 35-52. <https://doi.org/10.1590/S1677-04202005000100004>
- Sharma, R., & Kaur, R. (2018). Insights into fluoride-induced oxidative stress and antioxidant defences in plants. *Acta Physiologiae Plantarum*, 40, 181. <https://doi.org/10.1007/s11738-018-2754-0>
- Sharma, R., & Kaur, R. (2019). Fluoride toxicity triggered oxidative stress and the activation of antioxidative defence responses in *Spirodela polyrhiza* L. Schleiden. *Journal of Plant Interactions*, 14(1), 440-452. <https://doi.org/10.1080/17429145.2019.1646826>
- Sharma, R., Kumari, A., Rajput, S., Nishu, Arora, S., Rampal, R., & Kaur, R. (2019). Accumulation, morpho-physiological and oxidative stress induction by single and binary treatments of fluoride and low molecular weight phthalates in *Spirodela polyrhiza* L. Schleiden. *Scientific Reports*, 9, 20006. <https://doi.org/10.1038/s41598-019-56110-w>
- Sheldon, D., & Crimmin, M. (2022). Repurposing of F-gases: challenges and opportunities in fluorine chemistry. *Chemical Society Reviews*, 51(12), 4977-4995. <https://doi.org/10.1039/D1CS01072G>
- Singh, C.P., Bajpai, R., Singh, R.P., & Upreti, D.K. (2016). Improving bioclimatic envelop modeling for Lichens through remote sensing based substratum correction: A study over Indian Himalaya. *Cryptogam Biodiversity and Assessment*, 1(2), 1-19. <https://www.researchgate.net/publication/311464001>

- Singh, S., Kaur, I., & Kariyat, R. (2021). The multifunctional roles of polyphenols in plant-herbivore interactions. *International Journal of Molecular Sciences*, 22(3), 1442. <https://doi.org/10.3390/ijms22031442>
- Singh, S., Singh, J., & Singh, N. (2013). Studies on the impact of fluoride toxicity on growth parameters of *Raphanus Sativus* L. *Indian Journal of Scientific Research*, 4(1), 61-63
- Škvorová, Z., Černajová, I., Steinová, J., Peksa, O., Moya, P., & Škaloud, P. (2022). Promiscuity in lichens follows clear rules: Partner switching in *Cladonia* Is regulated by climatic factors and soil chemistry. *Frontiers in Microbiology*, 12. <https://doi.org/10.3389/fmicb.2021.781585>
- Sodani, R., Pandurangam, V., & Srivastava, J. (2021). Germination and morphological responses of *Triticum aestivum* L. to different concentrations of fluoride. *Environment Conservation Journal*, 22(3), 143-148 <https://doi.org/10.36953/ecj.2021.22318>
- Solárová, Z., Liskova, A., Samec, M., Kubatka, P., Büsselberg, D., & Solár, P. (2020). Anticancer potential of lichens' secondary metabolites. *Biomolecules*, 10(1), 87. <https://doi.org/10.3390/biom10010087>
- Song, K.S., & Williams, R.T. (1993). Alkaline earth fluorides. In: Self-Trapped Excitons. Springer Series in Solid-State Sciences, 105. Springer, Berlin, Heidelberg. [https://doi.org/10.1007/978-3-642-97432-8\\_4](https://doi.org/10.1007/978-3-642-97432-8_4)
- Stromsnes, K., Lagzdina, R., Olaso-Gonzalez, G., Gimeno-Mallench, L., & Gambini, J. (2021). Pharmacological properties of polyphenols: Bioavailability, mechanisms of action, and biological effects in In Vitro studies, Animal Models, and Humans. *Biomedicines*, 9(8), 1074. <https://doi.org/10.3390/biomedicines9081074>
- Subhashini, A., & Suganthi, R. (2014). Determination of toxic heavy metals in four different lichen species of Tamil Nadu, India. *Asian Journal of Biological and Life Sciences*, 3(1), 45-48
- Šujetovienė, G. (2015). Monitoring lichen as indicators of atmospheric quality. In: Upreti D., Divakar, P., Shukla, V., Bajpai, R. (eds), Recent Advances in Lichenology. Vol. 1. Modern methods and approaches in biomonitoring and bioprospection. Springer, New Delhi, 87, 118. [https://doi.org/10.1007/978-81-322-2181-4\\_4](https://doi.org/10.1007/978-81-322-2181-4_4)
- Šujetovienė, G., & Česynaitė, J. (2021). Assessment of air pollution at the indoor environment of a shooting range using lichens as biomonitors. *Journal of Toxicology and Environmental Health*, 84(7), 273-287. <https://doi.org/10.1080/15287394.2020.1862006>
- Šujetovienė, G., & Sliumpaitė, I. (2013). Effects of cadmium on physiological parameters of the lichen *Evernia prunastri* and *Ramalina fastigiata* In E3S Web of Conferences (Vol. 1). *EDP Sciences*. <https://doi.org/10.1051/e3sconf/20130129007>
- Šujetovienė, G., Smilgaitis, P., Dagiliūtė, R., & Žaltauskaitė, J. (2019). Metal accumulation and physiological response of the lichens transplanted near a landfill in central Lithuania. *Waste Management*, 85, 60-65. <https://doi.org/10.1016/j.wasman.2018.12.017>
- Sulaiman, N., Fuzy, S.F.F.M, Muis, S.I.N.A., & Ismail, B.S (2018). Use of lichens as bioindicators for determining atmospheric heavy metal concentration in Malaysia. *Pakistan Journal of Botany*, 50(1), 421-428
- Tak, Y. (2018). Catastrophic Effect of Fluoride in Plants: A Mini review. *Indian Research Journal of Genetics and Biotechnology*, 10(02), 222-227.
- Taiwo, I.E., Henry, A.N., Imbufe, A.P., & Adetoro, O.O., (2014). Heavy metal bioaccumulation and biomarkers of oxidative stress in the wild African tiger frog, *Hoplobatrachus occipitalis*. *African Journal of Environmental Science and Technology*, 8(1), 6-15. <https://doi.org/10.5897/AJEST2013.603>
- Talcott, P. (2018). Toxicologic Problems. In: Reed, S.M., Bayly, W.M., and Sellon, D.C. (eds.), Equine Internal Medicine (4<sup>th</sup> Ed.). France: Amazon, pp. 1460-1512, ISBN 9780323443296. <https://doi.org/10.1016/B978-0-323-44329-6.00021-8>
- Tarawneh, A.H., Salamon, I., Altarawneh, R., & Mitra, J. (2021). Assessment of lichens as biomonitors of heavy metal pollution in selected mining area, Slovakia. *Pakistan Journal of*

- Analytical and Environmental Chemistry*, 22(1), 53-59. <https://doi.org/10.21743/pjaec/2021.06.07>
- Tiwari, S., Tripathi, I.P., & Tiwari, H.L. (2013). Effects of lead on environment. *International Journal of Emerging Research in Management & Technology*, 2(6).
- Toto, A., Wild, P., Graille, M., Turcu, V., Crézé, C., Hemmendinger, M., Sauvain, J.J., Bergamaschi, E., Canu, I.G., & Hopf, N.B. (2022). Urinary malondialdehyde (MDA) concentrations in the general population-A systematic literature review and meta-analysis. *Toxics*, 10(4), 160. <https://doi.org/10.3390/toxics10040160>
- Tuladhar, P. Sasidharan, S., & Saudagar, P. (2021). 17 - Role of phenols and polyphenols in plant defense response to biotic and abiotic stresses. *Biocontrol Agents and Secondary Metabolites*, pp. 419-441. <https://doi.org/10.1016/B978-0-12-822919-4.00017-X>
- Ullah, S., Li, Z., Hassan, S., Ahmad, S., Guo, X., Wanghe, A., & Nabi, G., (2021). Heavy metals bioaccumulation and subsequent multiple biomarkers-based appraisal of toxicity in the critically endangered *Tor putitora*. *Ecotoxicology and Environmental Safety*, 228(1), 113032. <https://doi.org/10.1016/j.ecoenv.2021.113032>
- van Hulst, R.A., Muth, C-M., & Radermacher, P., (2008). Air embolism and diving injury. In: Papadakos, P.J. and Lachmann, B. (eds.), *Laraine Visser-Isles, Mechanical Ventilation*, W.B. Saunders, pp. 365-375. ISBN 9780721601861. <https://doi.org/10.1016/B978-0-7216-0186-1.50036-3>
- Vannini, A., Tedesco, R., Loppi, S., Di Cecco, V., Di Martino, L., Nascimbene, J., Dallo, F., & Barbante, C. (2021). Lichens as monitors of the atmospheric deposition of potentially toxic elements in high elevation Mediterranean ecosystems. *Science of The Total Environment*, 798, 149369. <https://doi.org/10.1016/j.scitotenv.2021.149369>
- Vardanyan, R.S., & Hruby, V.J. (2006). Antineoplastics. In: Vardanyan, R.S. and Hruby V.J. (eds.), *Synthesis of Essential Drugs*, France: Elsevier, pp. 389-418. ISBN 9780444521668. <https://doi.org/10.1016/B978-044452166-8/50030-3>
- Villa, A., Anabalon, M., Zohouri, V., Maguire, A., Franco, A.M., & Rugg-Gunn, A. (2010). Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: an analysis of available data. *Caries Research*, 44(1), 60-68.
- Vitikainen, O. (2009). William Nylander (1822-1899) and lichen chemotaxonomy. *The Bryologist*, 104, 263-267. [https://doi.org/10.1639/0007-2745\(2001\)104\[0263:WNALC\]2.0.CO;2](https://doi.org/10.1639/0007-2745(2001)104[0263:WNALC]2.0.CO;2)
- Walna, B., Kurzyca, I., & Siepak, J. (2007). Variations in fluoride level in precipitation in a region of human impact. *Water, Air, & Soil Pollution: Focus*, 7, 33-40. <https://doi.org/10.1007/s11267-006-9108-4>
- Wani, A.L., ARA, A., & Usmani, J.A. (2015). Lead toxicity: a review. *Interdisciplinary Toxicology*, 8(2), 55-64. <https://doi.org/10.1515/intox-2015-0009>
- Weaver, R. (1975). Lichens: mysterious and diverse, pp. 133-159. Corpus ID: 44411836
- Węgrzyn, M., Wietrzyk, P., Lisowska, M., Klimek, B., & Nicia, P. (2016). What influences heavy metals accumulation in arctic lichen *Cetrariella delisei* in Svalbard? *Polar Science*, 10(4), 532-540. <https://doi.org/10.1016/j.polar.2016.10.002>
- Whitford, G.M. (1996). The metabolism and toxicity of fluoride. *Monographs in Oral Science*, 16(2), 1-153
- Wieners, P.C., Mudimu, O., & Bilger, W. (2018). Survey of the occurrence of desiccation-induced quenching of basal fluorescence in 28 species of green microalgae. *Planta*, 248(3), 601-612. <https://doi.org/10.1007/s00425-018-2925-7>
- Winkler, A., Caricchi, C., Guidotti, M., Owczarek, M., Macrì, P., Nazzari, M., Amoroso, A., Di Giosa, A., & Listrani, S. (2019). Combined magnetic, chemical and morphoscopic analyses on lichens from a complex anthropic context in Rome. Italy. *Science of The Total Environment*, 690, 1355-1368. <https://doi.org/10.1016/j.scitotenv.2019.06.526>

- Yamazaki, T., Taguchi, T., & Ojima, I. (2009). 'Unique properties of fluorine and their relevance to medicinal chemistry and chemical biology', *Fluorine in Medicinal Chemistry and Chemical Biology*, pp. 3-46. <http://doi.org/10.1002/9781444312096.CHI>
- Yang, Y.N., Safarova, R.B., Park, S.Y., Sakuraba, Y., Oh, M., Zulfugarov, I.S., Lee, C.B., Tanaka, A., Paek, N., & Lee, C. (2019). Chlorophyll degradation and light-harvesting complex II aggregate formation during dark-induced leaf senescence in *Arabidopsis pheophytinase* mutants. *Journal of Plant Biology*, 62, 27-38. <https://doi.org/10.1007/s12374-018-0242-0>
- Yousuf, S., Choudhary, M.I., & Atta-ur-Rahman (2014). Chapter 7 - Lichens: Chemistry and biological activities. *Studies in Natural Products Chemistry*, 43, 2014, 223-259. <https://doi.org/10.1016/B978-0-444-63430-6.00007-2>
- Zhang, C., Yan, K., Fu, C., Peng, H., Craig, J., Hawker, C., & Whittaker, A. (2022a). Biological utility of fluorinated compounds: from materials design to molecular imaging, therapeutics and environmental remediation. *Chemical Reviews*, 122(1), 167-208. <https://doi.org/10.1021/acs.chemrev.1c00632>
- Zhang, J., Yu, G., Wen, W., Ma, X., Xu, B., & Huang, B. (2016). Functional characterization and hormonal regulation of the PHEOPHYTINASE gene LpPPH controlling leaf senescence in perennial ryegrass. *Journal of Experimental Botany*, 67, 935-945. <https://doi.org/10.1093/jxb/erv509>
- Zhang, H., Zhu, J., Gong, Z., & Zhu, J.K. (2022b). Abiotic stress responses in plants. *Nature Reviews Genetics*, 23(9), 104–119. <https://doi.org/10.1038/s41576-021-00413-0>
- Ziegler, E.E., Edwards, B.B., Jensen, R.L., Mahaffey, K.R., & Fomon, S.J. (1978). Absorption and retention of lead by infants. *Pediatric Research*, 12, 29-34. <https://doi.org/10.1203/00006450-197801000-00008>
- Zohoori, F.V., & Duckworth, R.M. (2017). Chapter 44 - Fluoride: Intake and metabolism, therapeutic and toxicological consequences. *Molecular, Genetic, and Nutritional Aspects of Major and Trace Minerals*, 539-550. <https://doi.org/10.1016/B978-0-12-802168-2.00044-0>
- Zounggran, Y., Lynda, E., Tchirioua, E., & Bieri, D.G. (2019). Effect of metal cations  $Pb^{2+}$ ,  $Cu^{2+}$ ,  $Zn^{2+}$ ,  $Mg^{2+}$  and  $Fe^{2+}$  on some physiological parameters of lichen *Parmotrema dilatatum*. *American Journal of Environmental Protection*, 7(1), 24-33. <https://doi.org/10.12691/env-7-1-5>
- Zulfiqar, U., Farooq, M., Hussain, S., Maqsood, M., Hussain, M., Ishfaq, M., Ahmad, M., & Anjum, M.Z. (2019). Lead toxicity in plants: Impacts and remediation. *Journal of Environmental Management*, 250, 109557. <https://doi.org/10.1016/j.jenvman.2019.109557>