International Journal of Life Science Research Archive

ISSN: 0799-6640 (Online)

Journal homepage: https://sciresjournals.com/ijlsra/

(Review Article)

Polyphosphates: Essential bioenergetic reservoirs and their role as critical nutrient depleters in biological systems

Kelvin E Vulla [1, *], Beatrice Francis [2], Richard S Komba [2] and Zabron Janes [2]

[1] *Department of Food Biotechnology and Nutritional Sciences, The Nelson Mandela African Institution of Science and Technology (NM-AIST), P.O. Box 447, Arusha, Tanzania.*
[2] *Department of Global Health and Biomedical Sciences, The Nelson Mandela African Institution of Science and Technology (NM-AIST), P.O. Box 447, Arusha, Tanzania.*

International Journal of Life Science Research Archive, 2025, 08(01), 019-032

Publication history: Received on 23 December 2024; revised on 02 February 2025; accepted on 05 February 2025

Article DOI: https://doi.org/10.53771/ijlsra.2025.8.1.0024

Abstract

Polyphosphates are linear polymers of inorganic phosphate that play a pivotal role in cellular bioenergetics and metabolism across a wide range of organisms. This review article explores the multifaceted functions of polyphosphates as essential bioenergetic reservoirs, highlighting their ability to store and release energy, thereby facilitating various biochemical processes. We discuss the synthesis and degradation pathways of polyphosphates, their influence on ATP metabolism, and their regulatory roles in cellular signaling and stress responses. Additionally, we examine how polyphosphates act as critical nutrient depleters in biological systems, impacting phosphate homeostasis. The interplay between polyphosphate metabolism and nutrient availability is scrutinized, with implications for microbial ecology, agricultural practices, and biotechnological applications. By integrating current research findings, this review emphasizes the significance of polyphosphates not only as energy reservoirs but also as key players in nutrient cycling and environmental sustainability, underscoring their importance in both basic and applied biological sciences.

Keywords: Polyphosphate; Bioenergetics; Adenosine Triphosphate; Nutrient depleters

1 Introduction

Polyphosphates are linear polymers composed of multiple phosphate residues, playing pivotal roles in a myriad of biological processes (Achbergerová & Nahálka, 2011). As essential bioenergetic reservoirs, polyphosphates not only serve as a primary energy source but also function as critical signaling molecules that influence cellular metabolism, growth, and differentiation (Rao et al., 2009; Achbergerová & Nahálka, 2011). Their unique structural properties enable them to store energy in a readily mobilizable form during periods of heightened metabolic demand, making them indispensable across a wide range of organisms, from prokaryotes to eukaryotes.

The structure of polyphosphate, as described by Achbergerová and Nahálka (2011) and illustrated in Figure 1, is characterized by a linear arrangement of phosphate groups linked by high-energy phosphoanhydride bonds. This polymeric form of inorganic phosphate exhibits notable biochemical versatility, playing crucial roles in various cellular processes, including energy metabolism, signaling pathways, and the regulation of enzymatic activity. The distinct structural features of polyphosphate not only contribute to its functional diversity within biological systems but also underscore its significance in microbiology and biotechnology.

* Corresponding author: Kelvin E Vulla

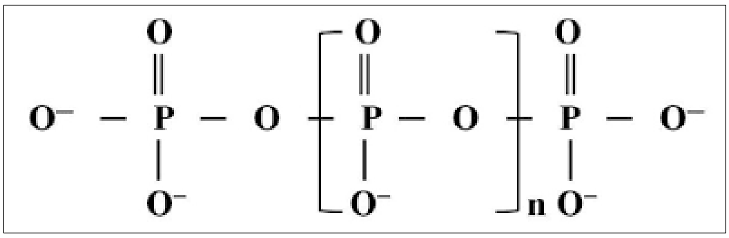

Figure 1 The structure of polyphosphate

The presence of phosphate compounds in biological materials has been documented since the 19th century, primarily through investigations into cellular biochemistry and the identification of ATP (adenosine triphosphate) as a key energy carrier (Walsh, 2020; Pasek & Kee, 2011). In the mid-20th century, researchers began to gain a deeper understanding of the significance of polyphosphate. While ATP and its derivatives were thoroughly studied, polyphosphates received comparatively less attention in the early stages. A pivotal moment in this field was the successful isolation and characterization of polyphosphates in microorganisms, marking a significant advancement in our comprehension of phosphate biology.

The 20th century witnessed significant advancements in chromatographic techniques, spectroscopy, and molecular biology methods, enabling scientists to accurately identify and investigate polyphosphate molecules. High-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) emerged as essential tools for elucidating the structure and function of these biomolecules within cells (Mopper et al., 2007; Seger et al., 2013). In addition, the development of genetic engineering and molecular biology techniques has allowed researchers to manipulate polyphosphate metabolism across various organisms. This progress has facilitated in-depth studies on the specific roles of polyphosphates in diverse biological contexts, including stress responses, biofilm formation, and metabolic regulation (Gray & Jakob, 2015; Downey, 2019; Bhalla et al., 2022).

Polyphosphates are vital components of cellular metabolism, serving as key molecular entities in a wide array of biochemical processes. These versatile polymers of phosphate function not only as energy reservoirs and phosphate donors but also play essential roles in regulatory and signaling pathways that modulate enzyme activity and metabolic pathways. Their involvement in critical cellular functions such as energy production, stress responses, and ion transport regulation underscores their importance in maintaining cellular homeostasis and viability. Recent studies indicate that polyphosphates hold promising therapeutic potential (Chaubal et al., 2003; Chen et al., 2023; Kulakovskaya et al., 2012; Schepler et al., 2021), positioning them as significant subjects for investigation in enhancing our understanding of cellular functions and developing innovative treatment strategies for various diseases. Thus, a deeper exploration of polyphosphates is likely to yield valuable insights into the intricate networks of cellular metabolism and their implications for health and disease.

This review reflects the growing recognition of polyphosphates in cellular functions, their ecological interactions, and their potential applications in health and industry. As research on polyphosphates continues to advance, it reveals intricate details regarding the complexity and significance of these molecules in the biological realm, further establishing their role as essential components in the overarching landscape of cellular biochemistry. Thus, polyphosphate research not only enhances our understanding of fundamental biological mechanisms but also opens avenues for potential biotechnological and therapeutic innovations.

2 Types of Polyphosphates

Polyphosphates can be classified into two main types: short-chain polyphosphates and long-chain polyphosphates. They differ significantly in their structure, solubility, and applications.

2.1 Short-Chain Polyphosphates

Short-chain polyphosphates consist of a limited number of phosphate groups, typically ranging from two to about ten units. Common examples include diphosphate (pyrophosphate, PPi) and triphosphate (ATP). Their structure involves a backbone of phosphate groups linked by oxygen atoms, which can exist in either linear or cyclic forms depending on the number of units. These polyphosphate chains are highly soluble in water. This solubility facilitates their role in biological processes, particularly in energy transfer and storage (Bonora et al., 2012). They serve critical functions in biochemistry, such as energy metabolism, nucleotide synthesis, and as signaling molecules. For instance, ATP is the primary energy currency in cells, participating in a variety of biochemical reactions (Ackerman & Tzagoloff, 2005).

Moreover, short-chain polyphosphates tend to undergo hydrolysis more readily than long-chain variants, releasing inorganic phosphate that can be reused in metabolic processes.

2.2 Long-Chain Polyphosphates

Long-chain polyphosphates consist of more than ten phosphate units, often extending into hundreds or thousands of phosphates. They can form branched or linear structures and may be synthesized through various chemical processes. Their molecular weight can vary significantly, influencing their physical and chemical properties. Long-chain polyphosphates are generally less soluble than short-chain polyphosphates and can form gel-like structures when concentrated. This property makes them useful in applications where thickening or gelling agents are needed (Franco et al., 2020). They are utilized in a range of applications, including fertilizers, food additives, water treatment, and detergents. In agriculture, they enhance nutrient retention in soil (Guelfi et al., 2022). Long-chain polyphosphates can be utilized as an energy source by various microorganisms in wastewater treatment processes, aiding in the removal of contaminants (Zhang et al., 2023). In biochemical contexts, long-chain polyphosphates can provide structural integrity to polysaccharides and enhance the functionality of certain enzymes and proteins (Azevedo & Reis, 2005).

3 Physicochemical Properties that Facilitate Polyphosphates Roles in Bioenergetics

Polyphosphates are linear or cyclic polymers of inorganic phosphate that play significant roles in bioenergetics, particularly in cellular energy storage and transfer processes. The following are physicochemical properties that facilitate their roles:

- High energy density. Polyphosphates, particularly long-chain polyphosphates, possess a high energy density due to the high-energy phosphoanhydride bonds that can be hydrolyzed to release energy (Pasek, 2019; Müller et al., 2019; Fontecilla-Camps, 2022). This property is crucial in energy metabolism as it provides readily accessible energy for various biochemical reactions.
- Hydrophilicity. The presence of multiple phosphate groups gives polyphosphates a hydrophilic nature, making them soluble in aqueous environments (Omelon & Grynpas, 2008). This solubility is essential for their mobilization and interaction with enzymes and other biomolecules in the cell.
- Polyanionic character. Polyphosphates are highly negatively charged due to the ionization of their phosphate groups. This polyanionic character allows them to participate in electrostatic interactions with positively charged biomolecules, such as proteins and metal ions, facilitating various metabolic processes (Çini & Ball, 2014; Semenyuk & Muronetz, 2019).
- Reactivity and versatility. According to Achbergerová & Nahálka (2011), polyphosphates can undergo various hydrolytic and phosphorylation reactions making them versatile in their biochemical functions. They can serve as donors for phosphate groups in phosphorylation reactions, which are crucial in multiple signaling pathways.
- Structural role. Polyphosphates can also contribute to the regulation of enzyme activities and the stabilization of protein structures (Albi & Serrano, 2016), possibly by functioning as structural scaffolds or as components of larger biological complexes.
- Biological compatibility. Polyphosphates are naturally occurring in many organisms and exhibit low toxicity, which makes them compatible with biological systems (Azevedo & Saiardi, 2017; Bowle et al., 2010; Desfougères et al., 2020; Borghi & Saiardi, 2023)). Their incorporation into cellular processes allows them to function without disrupting normal cellular functions.

3.1 Mechanisms of polyphosphate synthesis and degradation

Polyphosphate synthesis is primarily facilitated by enzymes known as polyphosphate kinases (PPKs), as illustrated in Figure 2. These enzymes catalyze the transfer of phosphate groups from ATP or other nucleoside triphosphates to the growing polyphosphate chains. In addition to PPKs, other kinases utilizing varied substrates also contribute to polyphosphate synthesis, highlighting the complexity and diversity of biochemical pathways involved in polyphosphate accumulation. The regulation of polyphosphate synthesis is intricately controlled by a variety of environmental and cellular signals, underscoring its significance in physiological adaptations and responses to stress (Riemer et al., 2022).

On the other hand, polyphosphate degradation is mediated by an array of enzyme systems, chiefly polyphosphatases and exopolyphosphatases, which degrade polyphosphate chains into shorter oligomers or release free inorganic phosphate. This hydrolytic process is crucial for the turnover of phosphate reserves and plays a key role in cellular signaling. The delicate equilibrium between synthesis and degradation is essential; dysregulation can lead to metabolic disorders and disrupt cellular homeostasis (Di Domenico & Lanzillotta, 2022). Furthermore, ongoing research is revealing additional roles of polyphosphates in modulating microbial physiology and influencing pathogenicity, indicating their importance beyond mere energy storage and as a source of phosphate. The mechanistic insights into both synthetic and degrading pathways offer promising avenues for targeted therapeutic strategies aimed at diseases linked to polyphosphate dysregulation (Travers, 2015).

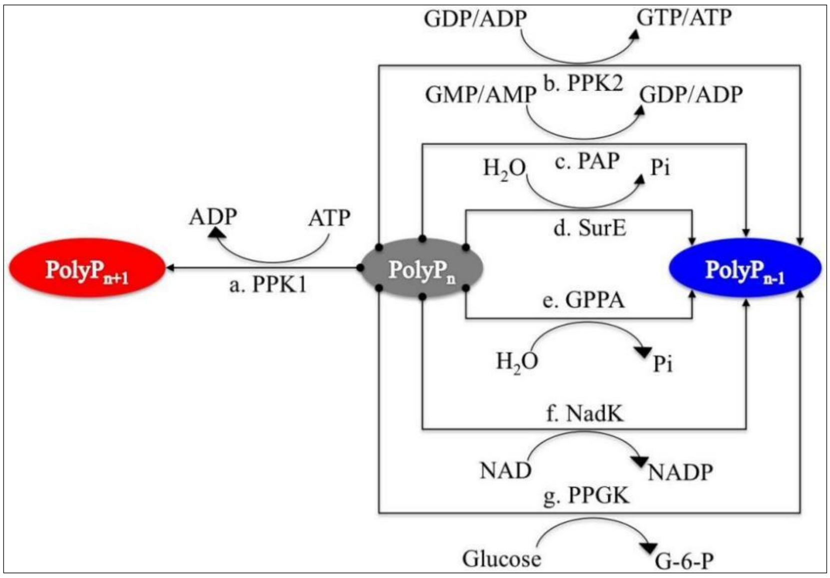

Figure 2 Schematic illustration of seven enzymes involved in polyphosphate synthesis (Wang et al., 2018). PPK1 represents the synthesis enzyme for polyP metabolism while other six enzymes, PPK2, PAP, SurE, GPPA, NadK, and PPGK, have preferences for polyP degradation although the reactions are reversible. Synthesis pathway is linked to red oval while degradation pathways have linkages with blue oval

3.2 Role of polyphosphates as energy reserves and their interaction with ATP

Polyphosphates (polyPs) are linear chains of inorganic phosphates (Pi) that play significant roles in various cellular processes, and are considered important intracellular energy reserves and have been shown to interact in various ways with adenosine triphosphate (ATP), the primary energy currency of the cell.

Polyphosphates serve as important energy reserves by storing energy in the form of phosphoanhydride bonds. When these bonds are hydrolyzed, they release inorganic phosphate and energy that can be utilized by the cell, particularly in conditions where ATP levels are low or during periods of cellular stress (Müller et al., 2019). In biochemical reactions, the hydrolysis of polyphosphates also releases energy that can drive various metabolic processes. For instance, they act as substrates for the phosphorylation of proteins and other biomolecules, thereby playing a critical role in signaling pathways and metabolic regulation (Cleland & Hengge, 2006). Additionally, in certain organisms, including bacteria and yeast, polyphosphates can enhance ATP utilization during times of high-energy demand. They facilitate the regeneration of ATP from ADP, thereby helping to sustain cellular energy levels (Sanz-Luque et al., 2020; Müller et al., 2019; Keasling et al., 2000; Kulaev et al., 1999).

The interaction between ATP and polyphosphates (polyPs) plays a crucial role in cellular metabolism due to their competitive binding to various enzymes, which can significantly affect metabolic processes. Elevated levels of polyPs can lead to a decrease in ATP availability, subsequently impairing essential cellular functions (McIntyre & Solesio, 2021; Solesio et al., 2021). Notably, certain enzymes that hydrolyze ATP can also utilize polyPs as substrates, allowing polyPs to modulate ATP availability by engaging in the same metabolic pathways. Furthermore, under specific conditions, polyphosphates may facilitate ATP synthesis through the action of polyphosphate-ATP kinases found in certain organisms (Sanz-Luque et al., 2020). This interplay between ATP and polyPs extends to cellular signaling pathways, where the relative levels of ATP and polyPs can influence various signaling cascades, thereby reflecting the cellular energy status and responding to environmental conditions (Borden et al., 2020).

3.3 Comparison of polyphosphate functions across different organisms

Polyphosphate (polyP) is a linear polymer composed of phosphate residues linked by alternating phosphoanhydride bonds. It plays a critical role in various biological processes across different organisms, including bacteria, fungi, plants, and animals. The functions of polyP can vary significantly depending on the organism and context, though some common roles can be highlighted.

3.3.1 Bacteria

In bacteria, polyphosphate (polyP) plays a crucial role in several essential functions, including energy storage. Polyphosphates serve as an energy reserve; when hydrolyzed, they release energy that can be harnessed for cellular metabolism (Morya et al., 2021). Additionally, polyP functions as a cofactor or regulator for various enzymes, thereby influencing metabolic pathways and physiological responses (Aceto et al., 2020). Furthermore, in response to environmental stresses such as nutrient deprivation, bacteria synthesize and accumulate polyP, which aids in their survival and adaptation (Foster, 2007).

3.3.2 Fungi

Fungi also utilize polyphosphate (polyP), although its functions in these organisms differ significantly from those observed in bacteria. One key role of polyP in fungi is in cellular signaling; it has been shown to be involved in various signaling pathways that influence gene expression and promote cell growth (Shin et al., 2016; Chiarella et al., 2020). Additionally, fungi use polyphosphate to sequester metal ions, which is essential for nutrient uptake and maintaining metal homeostasis within the cell (Albi & Serrano, 2016).

3.3.3 Plants

In plants, polyphosphate (polyP) plays multifaceted roles, including energy conservation and phosphate storage, similar to its functions in bacteria, particularly during stress conditions ((Lorenzo-Orts et al., 2020; Khan et al., 2023). Additionally, polyP is believed to be involved in cell signaling processes that regulate stomatal movement and other physiological responses (Seufferheld & Curzi, 2010). Furthermore, polyP influences root architecture and biochemistry, thereby supporting nutrient acquisition from the soil (Khan et al., 2023).

3.3.4 Animals

Polyphosphate (polyP) plays a significant role in various physiological processes in animals. In mammals, it is crucial for coagulation and hemostasis, acting as a procoagulant that facilitates platelet activation (Morrissey & Smith, 2015). Additionally, polyP is implicated in a range of cellular signaling pathways that influence cell proliferation and survival (Mutch, 2016). Furthermore, it may also contribute to bone mineralization processes, a process which is important in maintaining skeletal health (Morrissey & Smith, 2015).

3.4 Role of polyphosphates in signaling pathways and cellular responses

Polyphosphates play a crucial role in various signaling pathways and cellular responses across different organisms. These molecules serve as versatile signaling molecules that can modulate a range of biological processes, including cell growth, differentiation, and stress responses. In bacteria, for instance, polyphosphates are involved in the regulation of metabolic pathways and can act as a reservoir of inorganic phosphate, which is essential for ATP production and other cellular functions (Sanz-Luque et al., 2020). In eukaryotic cells, polyphosphates have been shown to influence intracellular signaling by interacting with proteins and influencing their activity. For example, polyphosphates can bind to kinases and phosphatases, thereby modulating phosphorylation states of target proteins, which is a critical mechanism in signal transduction (Kritmetapak & Kumar, 2021). Additionally, polyphosphates are implicated in the regulation of apoptosis and cell survival, as they can activate or inhibit key signaling pathways that determine cell fate (Brown & Kornberg, 2008). Recent studies have also highlighted their role in immune responses, where they can act as signaling molecules that modulate the activity of immune cells (Kus et al., 2022; Suess, 2022).

3.5 Interaction of polyphosphates with proteins and enzymes

Polyphosphates interact with proteins and enzymes, particularly kinases and phosphatases. The interaction can be discussed as follow;

3.5.1 Interaction with Kinases

Kinases are enzymes that catalyze the transfer of phosphate groups from high-energy donor molecules like ATP to specific substrates, typically proteins, thereby modulating their activity. Polyphosphates can enhance the activity of certain kinases by providing additional phosphate groups that serve as substrates or allosteric activators. In some cases, polyphosphates can stabilize the active conformation of kinases, facilitating their interaction with target proteins. This interaction can be critical in cellular signaling pathways where rapid phosphorylation is necessary for responding to external stimuli. Furthermore, polyphosphates can influence the specificity of kinases by altering their substrate recognition, potentially leading to different downstream effects depending on the polyphosphate chain length and structure.

3.5.2 Interaction with Phosphatases

On the other hand, phosphatases are enzymes that remove phosphate groups from proteins, effectively reversing the action of kinases. The interaction between polyphosphates and phosphatases can be complex. In some cases, polyphosphates may inhibit phosphatase activity by binding to the enzyme and preventing it from interacting with its substrate. This inhibition can lead to an accumulation of phosphorylated proteins, thereby amplifying signaling pathways that are dependent on phosphorylation states. Conversely, polyphosphates can also serve as substrates for certain phosphatases, further diversifying their roles in cellular signaling. The dynamic balance between kinases and phosphatases, influenced by polyphosphate interactions, is essential for maintaining cellular homeostasis and responding to environmental changes.

3.5.3 Regulatory Mechanisms

The regulatory mechanisms involving polyphosphates are multifaceted. The structure and length of polyphosphate chains can dictate their interaction with specific proteins and enzymes. For instance, shorter chains may preferentially interact with certain kinases, while longer chains may engage with phosphatases. This specificity can affect downstream signaling outcomes. Additionally, polyphosphate levels within the cell can fluctuate in response to metabolic changes, further modulating the activity of kinases and phosphatases. This intricate interplay suggests that polyphosphates act not merely as passive substrates but as active regulators of enzymatic activity, influencing various signaling cascades that govern cellular behavior.

3.5.4 Biological Implications

The implications of polyphosphate interactions with proteins and enzymes are significant in various biological contexts. For example, in the context of cancer, dysregulation of kinase and phosphatase activities can lead to uncontrolled cell growth. Understanding how polyphosphates influence these enzymes could provide insights into novel therapeutic approaches. Additionally, in microbial systems, polyphosphates are involved in stress responses, energy conservation, and biofilm formation. Their role in these processes underlines the evolutionary importance of polyphosphate interactions in both prokaryotic and eukaryotic organisms.

4 The role of polyphosphate in stress response and adaptation

Under stress conditions such as nutrient deprivation, oxidative stress, or extreme temperatures, cells mobilize polyP as a signaling molecule and energy reservoir. One of the primary functions of polyP is to modulate cellular processes, including the regulation of enzyme activities and the stabilization of proteins and nucleic acids. This adaptability is particularly vital for survival in fluctuating environments.

In bacteria, for instance, polyP accumulation is often observed during periods of phosphate starvation, allowing cells to store energy and maintain metabolic functions despite limited resources. PolyP also acts as a buffer against oxidative stress by scavenging reactive oxygen species, thereby protecting cellular components from damage. Furthermore, polyP influences the activation of stress-responsive pathways, such as the stringent response, which helps cells adapt to nutrient scarcity by altering gene expression and metabolic activities. In eukaryotic cells, polyP is involved in signaling cascades that promote cell survival and repair mechanisms in response to stress. Overall, polyphosphate serves as a multifunctional molecule that enhances cellular resilience, enabling organisms to adapt and thrive in challenging environmental conditions.

4.1 How polyphosphates depletes critical nutrients in biological systems

Polyphosphates can influence nutrient dynamics in biological systems, particularly in aquatic environments and soil ecosystems. The detailed explanation of how polyphosphates can deplete critical nutrients like phosphorus and nitrogen is explained as follow:

4.1.1 Nutrient Locking

Polyphosphates can bind to free phosphorus in the environment, forming complexes that are less bioavailable to organisms (Wang et al., 2019; Li et al., 2019). This "locking" mechanism can limit the availability of phosphorus for uptake by plants and microorganisms, which in turn affects overall productivity in ecosystems.

4.1.2 Microbial Competition

Polyphosphates can alter microbial community compositions by promoting the growth of certain microorganisms that can utilize these compounds efficiently (Mo et al., 2023; Weerasekara et al., 2016; Wang et al., 2018). This can lead to a competitive disadvantage for other organisms that rely on more traditional sources of phosphorus and nitrogen.

4.1.3 Eutrophication

In aquatic systems, the introduction of polyphosphates can lead to eutrophication, which is characterized by excessive nutrient loading. This can cause algal blooms that deplete oxygen levels when they die and decompose, leading to hypoxic conditions (Ortiz-Reyes & Anex, 2018; Ngatia & Taylor, 2018). This process can indirectly deplete nitrogen as well, as nitrogen-fixing microorganisms may be outcompeted or die off in low-oxygen conditions.

4.1.4 Chemical Reaction with Other Nutrients

Polyphosphates can react chemically with other nutrients, leading to precipitation or complexation (Wan et al., 2021). For instance, they can interact with calcium or magnesium, leading to the formation of insoluble compounds that are not accessible to plants and microbes.

4.1.5 Soil Dynamics

In soil systems, the addition of polyphosphates can influence soil chemistry and biology, potentially leading to nutrient imbalances. For example, soils may become more acidic or alkaline depending on the polyphosphate applied, affecting the solubility and availability of other nutrients, including nitrogen (Erel et al., 2023; Khourchi et al., 2023; Arai & Sparks, 2007).

5 Applications of Polyphosphates in Biotechnological Processes

Polyphosphates have significant applications in biotechnological processes, including bioremediation and bioproduction. These compounds have gained attention due to their unique chemical properties, biological functions, and their ability to store and release energy.

5.1 Bioremediation

Bioremediation is a critical process that utilizes microorganisms or plants to remove or neutralize environmental contaminants, and polyphosphates play several significant roles in enhancing this process (George & Wan, 2023; Raklami et al., 2022). Firstly, polyphosphates serve as a vital source of phosphate for microbial communities involved in bioremediation, as phosphate is essential for microbial growth and metabolism, thereby promoting the degradation of pollutants such as heavy metals and hydrocarbons (Aragaw, 2021). Additionally, certain microbes known as polyphosphate-accumulating organisms (PAOs) can utilize polyphosphates as an energy source, allowing them to thrive and enhance biodegradation processes through the release of phosphates during their metabolism (Ruiz-Haddad et al., 2024; Iorhemen et al., 2022). Furthermore, polyphosphates have the ability to chelate heavy metals, which increases their bioavailability for microbial uptake, thereby facilitating detoxification in contaminated environments where heavy metals may otherwise inhibit microbial activity (Zhou et al., 2022). Lastly, polyphosphates can promote biofilm formation, which is advantageous in bioremediation applications. Biofilms create a stable environment that supports microbial communities, enhancing their capacity to degrade pollutants effectively (Morya et al., 2021; Yadav & Chandra, 2020).

Overall, the incorporation of polyphosphates in bioremediation strategies can significantly improve the efficiency of contaminant degradation and detoxification.

5.2 Bioproduction

Bioproduction harnesses biological systems to generate valuable compounds, such as biofuels, bioplastics, and pharmaceuticals (Ogundele et al., 2024). Among these, polyphosphates play a crucial role in several applications. They serve as energy storage molecules in microbial systems, participating in ATP synthesis, the primary energy currency in cells, thereby enhancing the energy storage capacity of microorganisms and increasing biomass yields and production rates of desired compounds (Albi & Serrano, 2016). Additionally, polyphosphates can be utilized in the production of biodegradable plastics like polyhydroxyalkanoates (PHAs), as certain microorganisms can use polyphosphates as a carbon source, providing a sustainable alternative to petroleum-based plastics (Gomes Gradíssimo et al., 2020). Furthermore, polyphosphates can influence enzymatic activity and stability in biocatalytic processes, acting as cofactors or stabilizers that enhance enzyme performance in various bioprocesses (Li et al., 2020). According to Yin et al. (2024), metabolic engineering can also manipulate polyphosphate metabolism in microorganisms to optimize the production of specific metabolites, allowing for the diversion of metabolic flux towards the synthesis of valuable compounds.

6 Polyphosphates Potential in pharmaceutical developments and health applications

Polyphosphates, linear or cyclic polymers of phosphate units, have garnered significant attention in pharmaceutical developments and health applications due to their unique chemical properties and biological functionalities (Englert et al., 2018; Strasser & Teasdale, 2020). These compounds exhibit a range of beneficial effects, including their ability to modulate cellular signaling pathways, enhance drug delivery systems, and serve as biocompatible excipients in formulations. For instance, polyphosphates can act as carriers for therapeutic agents, improving their solubility and stability while facilitating targeted delivery to specific cell types, thereby minimizing side effects and enhancing therapeutic efficacy (Mahendran, 2020; Yilmaz & Jérôme, 2016). According to Müller et al. (2025), polyphosphates role in cellular metabolism and energy transfer makes them attractive candidates for applications in regenerative medicine and tissue engineering, where they can promote cell proliferation and differentiation. Furthermore, polyphosphates have been studied for their potential in vaccine formulation, acting as adjuvants that can elicit stronger immune responses (Khademi et al., 2018; Kovacs-Nolan et al., 2009). These diverse applications underscore the versatility of polyphosphates in modern medicine, highlighting the need for further research to fully exploit their potential in innovative therapeutic strategies.

6.1 Emerging Technologies for the Study of Polyphosphate

Recent advancements in genomic, proteomic, and metabolomic approaches have significantly enhanced our understanding of polyphosphate dynamics in various biological systems. Genomic techniques, such as next-generation sequencing, allow for the identification of genes involved in polyphosphate metabolism and transport, revealing the regulatory networks that govern their synthesis and degradation (Roy et al., 2021). Proteomic methods, including mass spectrometry, enable the characterization of proteins associated with polyphosphate metabolism, providing insights into their functional roles and interactions within cellular pathways (Varas et al., 2017; Guitart-Mampel et al., 2022). Additionally, metabolomic analyses facilitate the quantification of polyphosphate levels in various cellular environments, offering a comprehensive view of how these molecules influence metabolic processes. These emerging technologies not only assist in elucidating the biochemical pathways involving polyphosphate but also help to identify potential biomarkers for various diseases where polyphosphate dysregulation may play a role ((Brown, 2023; Da Costa & Solesio, 2024; Zareba et al., 2021; Peng et al., 2024).

6.2 Identified Knowledge Gaps and Potential Areas for Future Research

Despite significant progress in the study of polyphosphate, several knowledge gaps remain that need more investigation. One critical area is the understanding of the precise mechanisms by which polyphosphate interacts with other cellular components, including proteins and nucleic acids. Additionally, the role of polyphosphate in various cellular contexts, such as stress responses and cell signaling, is not yet fully understood. Moreover, the diversity of polyphosphate structures and their functional implications across different organisms presents an opportunity for comparative studies that could reveal conserved and unique features of polyphosphate metabolism. Future research could also explore the therapeutic potential of modulating polyphosphate levels in various diseases, including metabolic disorders and neurodegenerative diseases. These investigations underscore the need for a more integrated approach to polyphosphate research, combining insights from genomics, proteomics, and metabolomics to bridge the existing knowledge gaps.

6.3 The Importance of Interdisciplinary Research in Understanding Polyphosphate Dynamics

Interdisciplinary research plays a crucial role in advancing our understanding of polyphosphate dynamics, as it integrates diverse scientific disciplines such as molecular biology, biochemistry, and bioinformatics. By fostering collaboration among researchers with expertise in different areas, it becomes possible to develop comprehensive models that account for the complex interactions involving polyphosphate. For instance, combining genomic data with proteomic and metabolomic insights allows for a holistic view of polyphosphate function within cellular systems. This integrative approach not only enhances the accuracy of experimental findings but also facilitates the development of innovative methodologies and technologies for studying polyphosphate. Moreover, interdisciplinary research can lead to the discovery of novel applications of polyphosphate in biotechnology and medicine, particularly in areas such as drug delivery systems and biosensors. As the significance of polyphosphate continues to emerge in various fields, the collaboration between disciplines will be essential for uncovering the full potential of this fascinating molecule.

7 Conclusion

In conclusion, polyphosphates serve as vital bioenergetic reservoirs that play a crucial role in cellular metabolism and energy transfer. Their ability to store and release phosphate groups makes them indispensable in various biochemical pathways, supporting not only energy production but also the regulation of metabolic processes. However, the role of polyphosphates extends beyond energy storage; they are also critical nutrient depleters that can impact cellular homeostasis and nutrient availability. By influencing the dynamics of phosphorus in biological systems, polyphosphates affect ecosystem productivity and sustainability. Understanding the dual role of polyphosphates as both energy reservoirs and nutrient regulators provides valuable insights into their significance in physiology and ecology, highlighting the need for further research into their multifaceted functions and potential applications in biotechnology and environmental management

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no competing interests.

References

[1] Aceto, G. M., Catalano, T., & Curia, M. C. (2020). Molecular aspects of colorectal adenomas: the interplay among microenvironment, oxidative stress, and predisposition. *BioMed research international*, *2020*(1), 1726309. https://doi.org/10.1155/2020/1726309

[2] Achbergerová, L., & Nahálka, J. (2011). Polyphosphate-an ancient energy source and active metabolic regulator. *Microbial cell factories*, *10*, 1-14. https://doi.org/10.1186/1475-2859-10-63

[3] Ackerman, S. H., & Tzagoloff, A. (2005). Function, structure, and biogenesis of mitochondrial ATP synthase. *Progress in nucleic acid research and molecular biology*, *80*, 95-133. https://doi.org/10.1016/S0079-6603(05)80003-0

[4] Albi, T., & Serrano, A. (2016). Inorganic polyphosphate in the microbial world. Emerging roles for a multifaceted biopolymer. *World Journal of Microbiology and Biotechnology*, *32*, 1-12. https://doi.org/10.1007/s11274-015-1983-2

[5] Aragaw, T. A. (2021). Functions of various bacteria for specific pollutants degradation and their application in wastewater treatment: a review. *International Journal of Environmental Science and Technology*, *18*, 2063-2076. https://doi.org/10.1007/s13762-020-03022-2

[6] Arai, Y., & Sparks, D. L. (2007). Phosphate reaction dynamics in soils and soil components: A multiscale approach. *Advances in agronomy*, *94*, 135-179. https://doi.org/10.1016/S0065-2113(06)94003-6

[7] Azevedo, C., & Saiardi, A. (2017). Eukaryotic phosphate homeostasis: the inositol pyrophosphate perspective. *Trends in biochemical sciences*, *42*(3), 219-231.

[8] Azevedo, H. S., & Reis, R. L. (2005). Understanding the enzymatic degradation of biodegradable polymers and strategies to control their degradation rate. *Biodegradable systems in tissue engineering and regenerative medicine*, *1*, 177-201.

[9] Bhalla, K., Qu, X., Kretschmer, M., & Kronstad, J. W. (2022). The phosphate language of fungi. *Trends in microbiology*, *30*(4), 338-349. https://www.cell.com/trends/microbiology/abstract/S0966-842X(21)00187-6

[10] Bonora, M., Patergnani, S., Rimessi, A., De Marchi, E., Suski, J. M., Bononi, A., ... & Pinton, P. (2012). ATP synthesis and storage. *Purinergic signalling*, *8*, 343-357. https://doi.org/10.1007/s11302-012-9305-8

[11] Borden, E. A., Furey, M., Gattone, N. J., Hambardikar, V. D., Liang, X. H., Scoma, E. R., ... & Solesio, M. E. (2021). Is there a link between inorganic polyphosphate (polyP), mitochondria, and neurodegeneration?. *Pharmacological research*, *163*, 105211. https://doi.org/10.1016/j.phrs.2020.105211

[12] Borghi, F., & Saiardi, A. (2023). Evolutionary perspective on mammalian inorganic polyphosphate (polyP) biology. *Biochemical Society Transactions*, *51*(5), 1947-1956.

[13] Bowler, M. W., Cliff, M. J., Waltho, J. P., & Blackburn, G. M. (2010). Why did Nature select phosphate for its dominant roles in biology?. *New Journal of Chemistry*, *34*(5), 784-794. https://doi.org/10.1039/B9NJ00718K

[14] Brown, M. R., & Kornberg, A. (2008). The long and short of it–polyphosphate, PPK and bacterial survival. *Trends in biochemical sciences*, *33*(6), 284-290.

[15] Brown, R. B. (2023). Dysregulated phosphate metabolism in autism spectrum disorder: associations and insights for future research. *Expert Reviews in Molecular Medicine*, *25*, e20. https://doi.org/10.1017/erm.2023.15

[16] Chaubal, M. V., Gupta, A. S., Lopina, S. T., & Bruley, D. F. (2003). Polyphosphates and other phosphorus-containing polymers for drug delivery applications. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *20*(4).

[17] Chen, R., Huang, M., & Xu, P. (2023). Polyphosphate as an antithrombotic target and hemostatic agent. *Journal of Materials Chemistry B*, *11*(33), 7855-7872.

[18] Chiarella, E., Lombardo, N., Lobello, N., Aloisio, A., Aragona, T., Pelaia, C., ... & Mesuraca, M. (2020). Nasal polyposis: insights in epithelial-mesenchymal transition and differentiation of polyp mesenchymal stem cells. *International journal of molecular sciences*, *21*(18), 6878. https://doi.org/10.3390/ijms21186878

[19] Çini, N., & Ball, V. (2014). Polyphosphates as inorganic polyelectrolytes interacting with oppositely charged ions, polymers and deposited on surfaces: fundamentals and applications. *Advances in colloid and interface science*, *209*, 84-97. https://doi.org/10.1016/j.cis.2014.01.011

[20] Cleland, W. W., & Hengge, A. C. (2006). Enzymatic mechanisms of phosphate and sulfate transfer. *Chemical reviews*, *106*(8), 3252-3278. https://doi.org/10.1021/cr050287o

[21] Da Costa, R. T., & Solesio, M. E. (2024). Could mammalian inorganic polyphosphate be a crucial signaling molecule in neurological disorders?. *Neural Regeneration Research*, *19*(4), 701-702.

[22] Desfougères, Y., Saiardi, A., & Azevedo, C. (2020). Inorganic polyphosphate in mammals: where's Wally?. *Biochemical Society Transactions*, *48*(1), 95-101. https://doi.org/10.1042/BST20190328

[23] Di Domenico, F., & Lanzillotta, C. (2022). The disturbance of protein synthesis/degradation homeostasis is a common trait of age-related neurodegenerative disorders. *Advances in Protein Chemistry and Structural Biology*, *132*, 49-87.

[24] Downey, M. (2019). A stringent analysis of polyphosphate dynamics in Escherichia coli. *Journal of Bacteriology*, *201*(9), 10-1128. https://journals.asm.org/doi/full/10.1128/jb.00070-19

[25] Englert, C., Brendel, J. C., Majdanski, T. C., Yildirim, T., Schubert, S., Gottschaldt, M., ... & Schubert, U. S. (2018). Pharmapolymers in the 21st century: Synthetic polymers in drug delivery applications. *Progress in Polymer Science*, *87*, 107-164. https://doi.org/10.1016/j.progpolymsci.2018.07.005

[26] Erel, R., Yalin, D., Kushmaro-Bier, A., Li, Q., Gérard, F., & Toren, N. (2023). Soil properties and growing duration determine phosphorus phyto-availability dynamics of polyphosphate versus orthophosphate fertilizers. *Plant and Soil*, *485*(1), 299-315. https://doi.org/10.1007/s11104-022-05830-6

[27] Fontecilla-Camps, J. C. (2022). The complex roles of adenosine triphosphate in bioenergetics. *ChemBioChem*, *23*(10), e202200064. https://doi.org/10.1002/cbic.202200064

[28] Foster, P. L. (2007). Stress-induced mutagenesis in bacteria. *Critical reviews in biochemistry and molecular biology*, *42*(5), 373-397. https://doi.org/10.1080/10409230701648494

[29] Franco, D. F., De Oliveira Barud, H. G., Barud, H. S., Oliveira Junior, O. B., Meneguin, A. B., de Oliveira, L. F. C., ... & Nalin, M. (2020). A review on polyphosphate coacervates—Structural properties and bioapplications. *Journal of Sol-Gel Science and Technology*, *94*, 531-543. https://doi.org/10.1007/s10971-020-05228-9

[30] George, S. E., & Wan, Y. (2023). Microbial functionalities and immobilization of environmental lead: Biogeochemical and molecular mechanisms and implications for bioremediation. *Journal of Hazardous Materials*, *457*, 131738. https://doi.org/10.1016/j.jhazmat.2023.131738

[31] Gomes Gradíssimo, D., Pereira Xavier, L., & Valadares Santos, A. (2020). Cyanobacterial polyhydroxyalkanoates: A sustainable alternative in circular economy. *Molecules*, *25*(18), 4331. https://doi.org/10.3390/molecules25184331

[32] Gray, M. J., & Jakob, U. (2015). Oxidative stress protection by polyphosphate—new roles for an old player. *Current opinion in microbiology*, *24*, 1-6. https://doi.org/10.1016/j.mib.2014.12.004

[33] Guelfi, D., Nunes, A. P. P., Sarkis, L. F., & Oliveira, D. P. (2022). Innovative phosphate fertilizer technologies to improve phosphorus use efficiency in agriculture. *Sustainability*, *14*(21), 14266. https://doi.org/10.3390/su142114266

[34] Guitart-Mampel, M., Urquiza, P., Carnevale Neto, F., Anderson, J. R., Hambardikar, V., Scoma, E. R., ... & Solesio, M. E. (2022). Mitochondrial inorganic polyphosphate (polyP) is a potent regulator of mammalian bioenergetics in SH-SY5Y cells: a proteomics and metabolomics study. *Frontiers in Cell and Developmental Biology*, *10*, 833127. https://doi.org/10.3389/fcell.2022.833127

[35] Iorhemen, O. T., Ukaigwe, S., Dang, H., & Liu, Y. (2022). Phosphorus removal from aerobic granular sludge: Proliferation of polyphosphate-accumulating organisms (PAOs) under different feeding strategies. *Processes*, *10*(7), 1399. https://doi.org/10.3390/pr10071399

[36] Keasling, J. D., Van Dien, S. J., Trelstad, P., Renninger, N., & McMahon, K. (2000). Application of polyphosphate metabolism to environmental and biotechnological problems. *BIOCHEMISTRY C/C OF BIOKHIMIIA*, *65*(3), 324-331.

[37] Khademi, F., Derakhshan, M., Yousefi-Avarvand, A., & Tafaghodi, M. (2018). Potential of polymeric particles as future vaccine delivery systems/adjuvants for parenteral and non-parenteral immunization against tuberculosis: A systematic review. *Iranian journal of basic medical sciences*, *21*(2), 116. https://doi.org/10.22038/IJBMS.2017.22059.5648

[38] Khan, F., Siddique, A. B., Shabala, S., Zhou, M., & Zhao, C. (2023). Phosphorus plays key roles in regulating plants' physiological responses to abiotic stresses. *Plants*, *12*(15), 2861. https://doi.org/10.3390/plants12152861

[39] Khourchi, S., Delaplace, P., & Bargaz, A. (2023). Polyphosphate fertilizer use efficiency strongly relies on soil physicochemical properties and root-microbial activities. *Geoderma*, *429*, 116281. https://doi.org/10.1016/j.geoderma.2022.116281

[40] Kovacs-Nolan, J., Latimer, L., Landi, A., Jenssen, H., Hancock, R. E. W., & Babiuk, L. A. (2009). The novel adjuvant combination of CpG ODN, indolicidin and polyphosphazene induces potent antibody-and cell-mediated immune responses in mice. *Vaccine*, *27*(14), 2055-2064. https://doi.org/10.1016/j.vaccine.2009.01.117

[41] Kritmetapak, K., & Kumar, R. (2021). Phosphate as a signaling molecule. *Calcified tissue international*, *108*(1), 16-31. https://doi.org/10.1007/s00223-019-00636-8

[42] Kulaev, I. S., Kulakovskaya, T. V., Andreeva, N. A., & Lichko, L. P. (1999). Metabolism and function of polyphosphates in bacteria and yeast. *Inorganic Polyphosphates: Biochemistry, Biology, Biotechnology*, 27-43. https://doi.org/10.1007/s11274-015-1983-2

[43] Kulakovskaya, T. V., Vagabov, V. M., & Kulaev, I. S. (2012). Inorganic polyphosphate in industry, agriculture and medicine: Modern state and outlook. *Process Biochemistry*, *47*(1), 1-10. https://doi.org/10.1016/j.procbio.2011.10.028

[44] Kus, F., Smolenski, R. T., & Tomczyk, M. (2022). Inorganic polyphosphate—regulator of cellular metabolism in homeostasis and disease. *Biomedicines*, *10*(4), 913.

[45] Li, S., Guo, T., Guo, W., Cui, X., Zeng, M., & Wu, H. (2022). Polyphosphates as an effective vehicle for delivery of bioavailable nanoparticulate iron (III). *Food Chemistry*, *373*, 131477. https://doi.org/10.1016/j.foodchem.2021.131477

[46] Li, Z. L., Sun, C. Q., Qing, Z. L., Li, Z. M., & Liu, H. L. (2024). Engineering the thermal stability of a polyphosphate kinase by ancestral sequence reconstruction to expand the temperature boundary for an industrially applicable ATP regeneration system. *Applied and Environmental Microbiology*, *90*(2), e01574-23. https://doi.org/10.1128/aem.01574-23

[47] Lorenzo-Orts, L., Couto, D., & Hothorn, M. (2020). Identity and functions of inorganic and inositol polyphosphates in plants. *New Phytologist*, *225*(2), 637-652. https://doi.org/10.1111/nph.16129

[48] Mahendran, J. (2020). *Development of Calcium-Polyphosphate Particles for Therapeutic Delivery in the Joint* (Doctoral dissertation, Université d'Ottawa/University of Ottawa).

[49] McIntyre, B., & Solesio, M. E. (2021). Mitochondrial inorganic polyphosphate (polyP): The missing link of mammalian bioenergetics. *Neural Regeneration Research*, *16*(11), 2227-2228. https://doi.org/10.4103/1673-5374.310687

[50] Mo, S., He, S., Sang, Y., Li, J., Kashif, M., Zhang, Z., ... & Jiang, C. (2023). Integration of microbial transformation mechanism of polyphosphate accumulation and sulfur cycle in subtropical marine mangrove ecosystems with Spartina alterniflora invasion. *Microbial ecology*, *85*(2), 478-494. https://doi.org/10.1007/s00248-022-01979-w

[51] Mopper, K., Stubbins, A., Ritchie, J. D., Bialk, H. M., & Hatcher, P. G. (2007). Advanced instrumental approaches for characterization of marine dissolved organic matter: extraction techniques, mass spectrometry, and nuclear magnetic resonance spectroscopy. *Chemical Reviews*, *107*(2), 419-442. https://pubs.acs.org/doi/full/10.1021/cr050359b

[52] Morrissey, J. H., & Smith, S. A. (2015). Polyphosphate as modulator of hemostasis, thrombosis, and inflammation. *Journal of Thrombosis and Haemostasis*, *13*, S92-S97. https://doi.org/10.1111/jth.12896

[53] Morya, R., Tyagi, B., Sharma, A., & Thakur, I. S. (2021). Production and applications of polyphosphate. In *Biomass, Biofuels, Biochemicals* (pp. 283-307). Elsevier. https://doi.org/10.1016/B978-0-12-821888-4.00001-0

[54] Müller, W. E., Schröder, H. C., & Wang, X. (2019). Inorganic polyphosphates as storage for and generator of metabolic energy in the extracellular matrix. *Chemical reviews*, *119*(24), 12337-12374. https://doi.org/10.1021/acs.chemrev.9b00460

[55] Müller, W. E., Tolba, E., Schröder, H. C., & Wang, X. (2015). Polyphosphate: a morphogenetically active implant material serving as metabolic fuel for bone regeneration. *Macromolecular Bioscience*, *15*(9), 1182-1197. https://doi.org/10.1021/acs.chemrev.9b00460

[56] Mutch, N. J. (2016). Polyphosphate as a haemostatic modulator. *Biochemical Society Transactions*, *44*(1), 18-24. https://doi.org/10.1042/BST20150207

[57] Ngatia, L., & Taylor, R. (2018). Phosphorus eutrophication and mitigation strategies. *Phosphorus-recovery and recycling*, 45-61.

[58] Ogundele, O. D., Amoo, I. A., Adesina, A. O., Abidemi, A., & Bisi-Omotosho, A. (2024). Biotechnology for renewable fuel and chemicals. In *Microbial Biotechnology for Bioenergy* (pp. 325-345). Elsevier. https://doi.org/10.1016/B978-0-443-14112-6.00016-X

[59] Omelon, S. J., & Grynpas, M. D. (2008). Relationships between polyphosphate chemistry, biochemistry and apatite biomineralization. *Chemical reviews*, *108*(11), 4694-4715. https://doi.org/10.1021/cr0782527

[60] Ortiz-Reyes, E., & Anex, R. P. (2018). A life cycle impact assessment method for freshwater eutrophication due to the transport of phosphorus from agricultural production. *Journal of Cleaner Production*, *177*, 474-482. https://doi.org/10.1016/j.jclepro.2017.12.255

[61] Pasek, M. A. (2019). Thermodynamics of prebiotic phosphorylation. *Chemical reviews*, *120*(11), 4690-4706. https://doi.org/10.1021/acs.chemrev.9b00492

[62] Pasek, M. A., & Kee, T. P. (2011). On the origin of phosphorylated biomolecules. In *Origins of life: the primal self-organization* (pp. 57-84). Berlin, Heidelberg: Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-21625-1_3

[63] Peng, J., Feinstein, D., DeSimone, S., & Gentile, P. (2024). A Review of the Tear Film Biomarkers Used to Diagnose Sjogren's Syndrome. *International Journal of Molecular Sciences*, *25*(19), 10380. https://doi.org/10.3390/ijms251910380

[64] Raklami, A., Meddich, A., Oufdou, K., & Baslam, M. (2022). Plants—Microorganisms-based bioremediation for heavy metal cleanup: Recent developments, phytoremediation techniques, regulation mechanisms, and molecular responses. *International Journal of Molecular Sciences*, *23*(9), 5031. https://doi.org/10.3390/ijms23095031

[65] Rao, N. N., Gómez-García, M. R., & Kornberg, A. (2009). Inorganic polyphosphate: essential for growth and survival. *Annual review of biochemistry*, *78*(1), 605-647. https://doi.org/10.1146/annurev.biochem.77.083007.093039

[66] Riemer, E., Pullagurla, N. J., Yadav, R., Rana, P., Jessen, H. J., Kamleitner, M., ... & Laha, D. (2022). Regulation of plant biotic interactions and abiotic stress responses by inositol polyphosphates. *Frontiers in plant science*, *13*, 944515. https://doi.org/10.3389/fpls.2022.944515

[67] Roy, S., Guanglei, Q., Zuniga-Montanez, R., Williams, R. B., & Wuertz, S. (2021). Recent advances in understanding the ecophysiology of enhanced biological phosphorus removal. *Current Opinion in Biotechnology*, *67*, 166-174. https://doi.org/10.1016/j.copbio.2021.01.011

[68] Ruiz-Haddad, L., Ali, M., Pronk, M., van Loosdrecht, M. C., & Saikaly, P. E. (2024). Demystifying polyphosphate-accumulating organisms relevant to wastewater treatment: A review of their phylogeny, metabolism, and detection. *Environmental Science and Ecotechnology*, 100387. https://doi.org/10.1016/j.ese.2024.100387

[69] Sanz-Luque, E., Bhaya, D., & Grossman, A. R. (2020). Polyphosphate: a multifunctional metabolite in cyanobacteria and algae. *Frontiers in Plant Science*, *11*, 938. https://doi.org/10.3389/fpls.2020.00938

[70] Schepler, H., Wang, X., Neufurth, M., Wang, S., Schroeder, H. C., & Mueller, W. E. (2021). The therapeutic potential of inorganic polyphosphate: A versatile physiological polymer to control coronavirus disease (COVID-19). *Theranostics*, *11*(13), 6193. https://doi.org/10.7150/thno.59535

[71] Seger, C., Sturm, S., & Stuppner, H. (2013). Mass spectrometry and NMR spectroscopy: modern high-end detectors for high resolution separation techniques–state of the art in natural product HPLC-MS, HPLC-NMR, and CE-MS hyphenations. *Natural product reports*, *30*(7), 970-987. https://doi.org/10.1039/C3NP70015A

[72] Semenyuk, P., & Muronetz, V. (2019). Protein interaction with charged macromolecules: From model polymers to unfolded proteins and post-translational modifications. *International Journal of Molecular Sciences*, *20*(5), 1252. https://doi.org/10.3390/ijms20051252

[73] Seufferheld, M. J., & Curzi, M. J. (2010). Recent discoveries on the roles of polyphosphates in plants. *Plant molecular biology reporter*, *28*, 549-559. https://doi.org/10.1007/s11105-010-0187-z

[74] Shin, S. H., Ye, M. K., Kim, Y. H., & Kim, J. K. (2016). Role of TLRs in the production of chemical mediators in nasal polyp fibroblasts by fungi. *Auris Nasus Larynx*, *43*(2), 166-170. https://doi.org/10.1016/j.anl.2015.07.003

[75] Solesio, M. E., Xie, L., McIntyre, B., Ellenberger, M., Mitaishvili, E., Bhadra-Lobo, S., ... & Pavlov, E. V. (2021). Depletion of mitochondrial inorganic polyphosphate (polyP) in mammalian cells causes metabolic shift from oxidative phosphorylation to glycolysis. *Biochemical Journal*, *478*(8), 1631-1646. https://doi.org/10.1042/BCJ20200975

[76] Strasser, P., & Teasdale, I. (2020). Main-chain phosphorus-containing polymers for therapeutic applications. *Molecules*, *25*(7), 1716. https://doi.org/10.3390/molecules25071716

[77] Suess, P. M. (2022). Effects of polyphosphate on leukocyte function. *Inorganic Polyphosphates: From Basic Research to Medical Application*, 131-143. https://doi.org/10.1007/978-3-031-01237-2_6

[78] Travers, R. (2015). *Polyphosphate is a novel modulator of coagulation and inflammation and is a therapeutic target* (Doctoral dissertation, University of Illinois at Urbana-Champaign).

[79] Varas, M., Valdivieso, C., Mauriaca, C., Ortíz-Severín, J., Paradela, A., Poblete-Castro, I., ... & Chávez, F. P. (2017). Multi-level evaluation of Escherichia coli polyphosphate related mutants using global transcriptomic, proteomic and phenomic analyses. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *1861*(4), 871-883. https://doi.org/10.1016/j.bbagen.2017.01.007

[80] Walsh, C. T. (2020). *The chemical biology of phosphorus* (Vol. 13). Royal Society of Chemistry.

[81] Wan, B., Yang, P., Jung, H., Zhu, M., Diaz, J. M., & Tang, Y. (2021). Iron oxides catalyze the hydrolysis of polyphosphate and precipitation of calcium phosphate minerals. *Geochimica et Cosmochimica Acta*, *305*, 49-65. https://doi.org/10.1016/j.gca.2021.04.031

[82] Wang, H., Teng, C., Li, H., Sun, X., Jiang, C., Lou, L., ... & Zhang, Z. (2018). Microbial community shifts trigger loss of orthophosphate in wetland soils subjected to experimental warming. *Plant and Soil*, *424*, 351-365. https://doi.org/10.1007/s11104-017-3538-9

[83] Wang, L., Yan, J., Wise, M. J., Liu, Q., Asenso, J., Huang, Y., & Tang, D. (2018). Distribution patterns of polyphosphate metabolism pathway and its relationships with bacterial durability and virulence. *Frontiers in Microbiology*, *9*, 782. https://doi.org/10.3389/fmicb.2018.00782

[84] Wang, X., Gao, Y., Hu, B., & Chu, G. (2019). Comparison of the hydrolysis characteristics of three polyphosphates and their effects on soil phosphorus and micronutrient availability. *Soil Use and Management*, *35*(4), 664-674. https://doi.org/10.1111/sum.12526

[85] Weerasekara, A. W., Jenkins, S., Abbott, L. K., Waite, I., McGrath, J. W., Larma, I., ... & Whiteley, A. S. (2016). Microbial phylogenetic and functional responses within acidified wastewater communities exhibiting enhanced phosphate uptake. *Bioresource technology*, *220*, 55-61. https://doi.org/10.1016/j.biortech.2016.08.037

[86] Yadav, S., & Chandra, R. (2020). Biofilm-mediated bioremediation of pollutants from the environment for sustainable development. In *New and future developments in microbial biotechnology and bioengineering: microbial biofilms* (pp. 177-203). Elsevier. https://doi.org/10.1016/B978-0-444-64279-0.00014-1

[87] Yilmaz, Z. E., & Jérôme, C. (2016). Polyphosphoesters: New trends in synthesis and drug delivery applications. *Macromolecular bioscience*, *16*(12), 1745-1761. https://doi.org/10.1002/mabi.201600269

[88] Yin, L., Zhou, Y., Ding, N., & Fang, Y. (2024). Recent Advances in Metabolic Engineering for the Biosynthesis of Phosphoenol Pyruvate–Oxaloacetate–Pyruvate-Derived Amino Acids. *Molecules*, *29*(12), 2893. https://doi.org/10.3390/molecules29122893

[89] Zareba, L., Szymanski, J., Homoncik, Z., & Czystowska-Kuzmicz, M. (2021). Evs from balf—Mediators of inflammation and potential biomarkers in lung diseases. *International journal of molecular sciences*, *22*(7), 3651. https://doi.org/10.3390/ijms22073651

[90] Zhang, Y., Qiu, X., Luo, J., Li, H., How, S. W., Wu, D., ... & Lu, H. (2023). A review of the phosphorus removal of polyphosphate-accumulating organisms in natural and engineered systems. *Science of The Total Environment*, 169103. https://doi.org/10.1016/j.scitotenv.2023.169103

[91] Zhou, B., Zhang, T., & Wang, F. (2023). Microbial-based heavy metal bioremediation: Toxicity and eco-friendly approaches to heavy metal decontamination. *Applied Sciences*, *13*(14), 8439. https://doi.org/10.3390/app13148439.