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Phosphorus Compounds in Pharmaceutical Drugs and Their Rising Role as Antioxidants and Antidiabetics: A Review

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Abstract
Phosphorus compounds in general and phosphonates in particular, are a corner stone in pharmaceutical drugs. Many of these compounds exhibit antifungal, antibacterial, anticancer and significant analgesic/antiinflammatory properties. Bisphosphonates and aminophosphonates, taken as representative examples, are important precursors of the corresponding bisphosphonic acid with, in many cases, remarkable pharmacologically interesting properties. The benefits of these compounds use in the prevention of bone mass loss in addition to their antitumor potential when used in the adjuvant setting were approved in many literatures. This article aims to shed light on phosphorus compounds as rising stars in pharmaceutical drugs in addition to their increasing role as antioxidants and antidiabetics. The available body of clinical trials supporting the use of these compounds in this setting was briefly scrutinized. These results recommended for a careful consideration of the role that phosphorus compounds can act as a new generation of antioxidants and antidiabetics. The emphasis is on the recent information added to this topic. Although the author has attempted the review to be encyclopedic with respect to the topics, the article is not exhaustive.

1. Introduction

Phosphorus is essential to life and its derivatives are used in a multitude of technical/industrial applications. Today the main source of phosphorus worldwide is based on mining of phosphate rocks. This natural resource is limited because natural phosphorus cycle is very long. Practically, it cannot be considered as being renewable. Nowadays, there is a need to switch to more phosphorus resources. A phosphorus heterocyclic system in particular, continues to be one of the most active areas for research. Phosphonates are one of the three sources of phosphate intake in biological cells; the other two are inorganic phosphates and organophosphates[1].

2. Phosphorus Compounds in Pharmaceutical Drugs

Phosphonates or phosphonic acids are organ phosphorus compounds containing C-PO(OH)$_2$ or C-PO(OR)$_2$ groups (where R=alkyl, aryl). They are quite common among different organisms, from prokaryotes to eubacteria as well as, fungi, mollusks, insects, and others[1-4].

It has been proved in many literatures[5-8] that, the introduction of the phosphor moiety into *N*- and/or *S*-heterocycles enhances, usually the biological and pharmacological activities.

Some phosphonates exhibit antifungal[5], antibacterial[6] and anticancer activity[7]. Many commercially important compounds are phosphonates, including: Glyphosate, the herbicide "Roundup" and Ethephon, a widely used plant growth regulator. Despite the structural and electronic differences between the phosphonate- and carboxylic functionalities (in terms of size, shape, acidity, and geometry), the phosphonate is regarded as a bioisostere of the carboxylic group[8]. The biological role of the natural phosphonates is still poorly understood.

2.1. Bisphosphonates

2.1.1. History

Bisphosphonates(BPs) were developed in the 19th century but were first investigated in the 1960s for use in disorders of bone metabolism. In oncology[9-14], the introduction of BP therapy since 1969 has radically improved the management and prevention of skeletal related events (SREs) associated with malignancy disseminated to the bones, including pathologic fractures, bone pain, impaired mobility, spinal cord compression, and hypercalcemia[10-14]. In addition to inhibiting bone resorption, bisphosphonates (BPs) have also been shown to exhibit antitumor effects such as inhibition of proliferation and induction of apoptosis in cultured human breast cancer cells. Recent studies reported that BP- drug treatment interferes with breast cancer cell adhesion to bone matrix and inhibit cell migration and invasion[9].

2.1.2. Chemistry

Bis- or polyphosphonates have not been found to occur naturally. There are a great number of reports on the preparation and biochemical studies on such compounds[15-36]. The bisphosphonates (BPs) are synthetic organic compounds characterized by a P-C-P backbone structure. They are called bisphosphonates because they have two phosphonate (PO_3) groups. They are chemically stable analogues of the endogenous metabolites, inorganic pyrophosphates (PPi) (Fig. 1). The P–C–P structure allows a great number of possible variations, mostly by changing the two lateral chains on the carbon. Small changes in the structure of the bisphosphonates can lead to extensive alterations in their physicochemical, biological, therapeutic, and toxicological characteristics.

Unlike PPi, BPs are resistant to breakdown by enzymatic hydrolysis, due to a carbon atom bridging the two phosphonate groups.

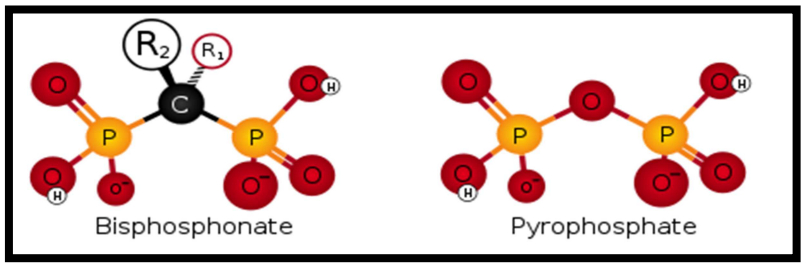


Fig 1. *The analogue structures of bisphosphonate & pyrophosphate (From Wikipedia, the free encyclopedia).*

2.1.3. Pharmacological Studies

Bisphosphonates (BPs) (also called diphosphonates) are a class of drugs that prevent the loss of bone mass[17].

Table 1. *Potency of various BP-drugs relative to that of etidronate.*

BP-Drug	Potency relative to etidronate
Etidronate (Didronel)	1
Clodronate (Bonefos, Loron)	10
Tiludronate (Skelid)	10
Pamidronate (APD, Aredia)	100
Neridronate (Nerixia)	100
Olpadronate	500
Alendronate (Fosamax)	500
Ibandronate (Boniva)	1000
Risedronate (Actonel)	2000
Zoledronate (Zometa, Aclasta)	10000

The biological effects of BPs on calcium metabolism were originally ascribed to their physicochemical effects to impede the dissolution of hydroxyapatite crystals[18]. Moreover, R^1 substituent, such as hydroxyl or amino group, enhances chemisorption to bone mineral, while R^2 substituent results in variations in the antiresorptive potency of several orders of magnitude. The antiresorptive potency[19] (Table 1) observed with the different R^2 groups in different BPs is thought to be linked to their effects on biochemical activity, for example, inhibition of the enzyme farnesyl pyrophosphate synthase (FPPS), and to their ability to bind to hydroxyapatite. Many bisphosphonates have been investigated in humans with respect to their effects on bone, and a lot of them are commercially available today for treatment of bone disease[19].

The uses of bisphosphonates were discussed in many litreatures[17-36]. They include the prevention and treatment of osteoporosis, osteitisdeformans ("Paget's disease of bone"), as they inhibit the digestion of bone by encouraging osteoclasts to undergo apoptosis, or cell death, thereby slowing bone loss, bone metastasis (with or without hypercalcaemia), multiple myeloma, primary hyperparathyroidism, osteogenesisimperfecta, fibrous dysplasia, and other conditions that feature bone fragility. One of their non-medical uses was to soften water in irrigation systems used in orange groves.

The use of bisphosphonates in cancers can also be traced back to the early 1980s. Several groups showed the impressive efficacy, particularly of clodronate[22,23] and pamidronate[24],in

the treatment of hypercalcaemia of malignancy, associated with myeloma and bone metastases. However, it took many more years before the large-scale trials were done that enabled the registration of these drugs for the prevention of skeletal related events associated with a variety of cancers[25].

Clezardin et al.[28], in their accompanying review of the scientific basis of using BPs in cancers, discuss the relative contribution of direct antitumour effects versus effects mediated through inhibition of bone resorption. An exciting possibility is that synergistic antitumour effects may be achievable in the presence of other chemotherapeutic agents. In this context, the recent studies carried out by Abdou et. al.[29-36] have been directed toward the construction of bioactive heterocycle gem-diphosphor esters, especially those associated with antitumor[30,31], antiinflammatory[32-35], and antiosteoporosis potencies[29, 32-36].

2.1.4. Mode of Action

The initial rationale for BPs use in humans was their potential in preventing the dissolution of hydroxylapatite, the principal bone mineral, thus arresting bone loss. Their actual mechanism of action was only demonstrated with the initial launch of Fosamax (Alendronate) by Merck & Co. Bisphosphonates' mechanisms of action all stem from their structures' similarity to pyrophosphate (see Fig. 1), thereby inhibiting activation of enzymes that utilize pyrophosphate. Bisphosphonate-based drugs' specificity comes from the two phosphonate groups (and possibly a hydroxyl at R^1) that work together to coordinate calcium ions. Bisphosphonate molecules preferentially "stick" to calcium and bind to it. The largest store of calcium in the human body is in bones, so they accumulate to a high concentration only in bones[17].

In Figure 2, the stages of uptake and release of bisphosphonates from bone are illustrated[20] as follows: Oral or intravenously administered bisphosphonates bind to bone mineral. a) Liberated during bone resorption, bisphosphonates are taken up by osteoclasts. b) After engulfing bisphosphonates, osteoclasts undergo changes, including loss of ruffled border, and become inactive, preventing further resorption. c) Eventually, osteoclasts detach from bone surface and can persist in bone marrow as large, multinucleated inactive cells, while the resorption lacuna is filled with new bone. d) After treatment discontinuation, new bone remodeling cycles can release embedded bisphosphonates. Uptake of these compounds by osteoclasts results in decreased resorption. e) Bisphosphonates might also be released from bone by desorption, at a rate dependent on their binding affinity.

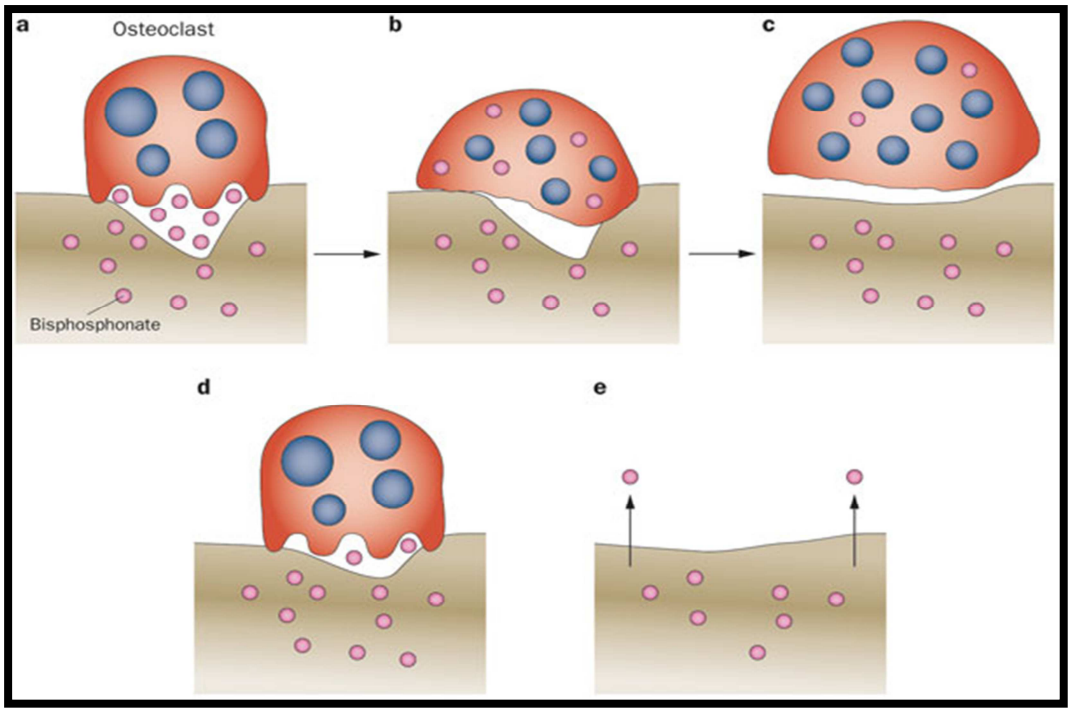


Fig 2. *Uptake and release of bisphosphonates from bone (Papapoulos, 2013)[20].*

There are two classes of bisphosphonates that work differently in killing osteoclast cells: (i) Non-*N*-containing bisphosphonates including: Etidronate (Didronel), Clodronate (Bonefos, Loron), Tiludronate (Skelid). They are metabolised in the cell to compounds that replace the terminal pyrophosphate moiety of ATP, forming a nonfunctional molecule that competes with adenosine triphosphate (ATP) in the cellular energy metabolism. The osteoclast initiates apoptosis and dies, leading to an overall decrease in the breakdown of bone. (ii) *N*-containing bisphosphonates including: Pamidronate (APD, Aredia), Neridronate (Nerixia), Alendronate (Fosamax), Ibandronate (Boniva), Risedronate (Actonel), Zoledronate (Zometa, Aclasta). They act on bone metabolism by binding and blocking the enzyme farnesylpyrophosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway,

Fig. 3)[27]. They interfere with FPPS enzyme and geranylgeranyl pyrophosphate synthase (GGPPS), two key enzymes in the mevalonate pathway. As a consequence, the disruption of the mevalonate pathway by *N*-BPs results in the accumulation of isopentenyl pyrophosphate (IPP), which is then converted to a cytotoxic ATP analogue called ApppI.

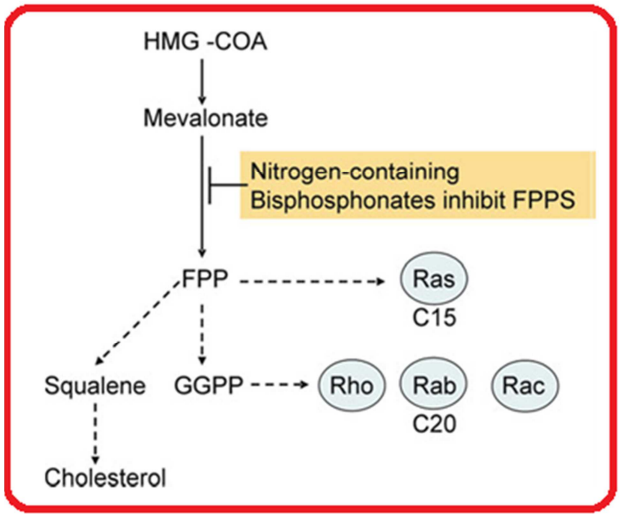
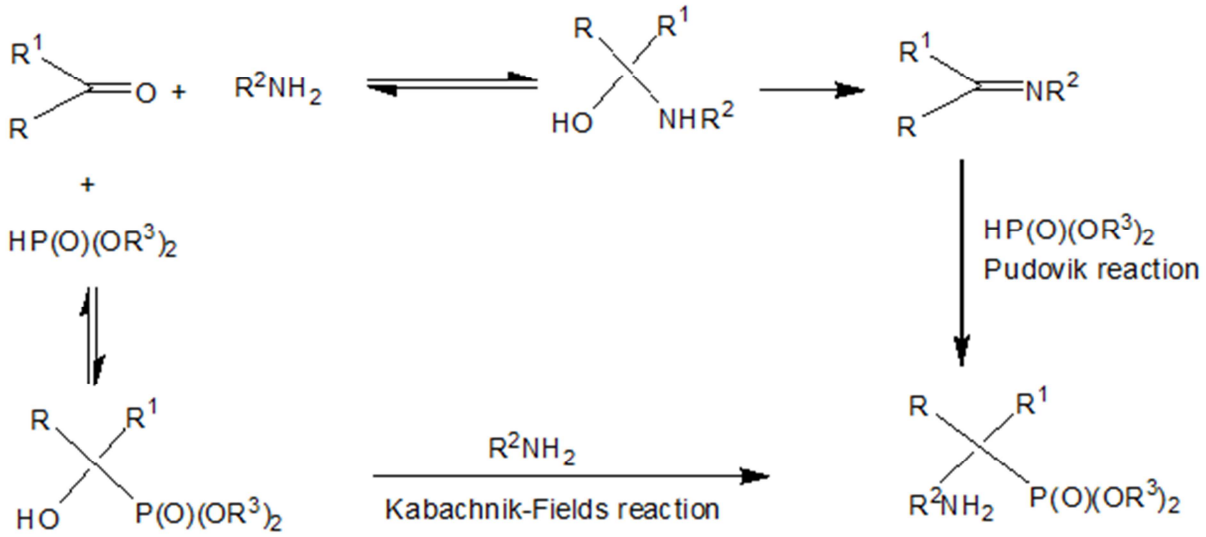


Fig 3. *N-BPs interfere with FPPS and GGPPS in the mevalonate pathway (From Wikipedia, the free encyclopedia).*

2.2. Aminophosphonates: History, Chemistry & Pharmacological Applications

The naturally-occurring phosphonate 2-aminoethylphosphonic acid was first identified in 1959 in plants and many animals, where it is localized in membranes. Aminophosphonates have been the focus of attention in recent years because of their structural analogy to the corresponding α-aminoacids as well as heterocyclic phosphonates[37,38] and ω-aminophosphonates[39], which have found a wide range of applications in agricultural and medicinal chemistry[40-43].

Several approaches[44] have been developed for the synthesis of α-aminophosphonates (Scheme 1). Two main pathways are: (i) Kabachnik–Fields, multi components one pot reaction, in which a carbonyl, an amine and a di- or tri-alkyl phosphite react in a single-pot; (ii) Pudovik reaction, in which the key step is the nucleophilic addition of amine to a carbonyl compound followed by addition of a dialkyl (or diaryl) phosphite to the resulting imine. In some reports, these reactions were carried out in straight-forward one-pot procedure without any catalysts[45,46] while, in most cases, it was performed using catalysts[47-50].



Scheme 1. *Synthesis of aminophosphonates (Prasad, 2003).*

As part of their research program on the synthesis of *α*- and *β*-aminophosphonates, Abdou, et. al.[51-56], have reported a modified multi-components reaction in a one-pot synthesis, to give substituted *N*-heteocyclicaminomethylene diphosphonates, in high rates[52]. In most cases, the synthesized phosphorus compounds (mono- or diphosphonates and/or phosphonic acids) showed significant analgesic/antiinflammatory properties. Particularly remarkable is their anticancer activity[51-57].

Aminophosphonic acid derivatives can serve as haptens in catalytic enzyme antibody generation and as transition-state analogues for, e.g. peptide coupling reactions and peptide hydrolysis[8], making them important targets in the development of new enzyme inhibitors[58-60]. In sequel, the versatile research directed toward the synthesis of *α*- and *β*-aminophosphonic acids has resulted in a new class of drugs and other bioactive compounds with a great variety of commercial applications, ranging from medicine to agriculture[7,61,62].

3. Phosphorus Compounds as Antioxidants

Oxidative stress" as a concept in redox biology and

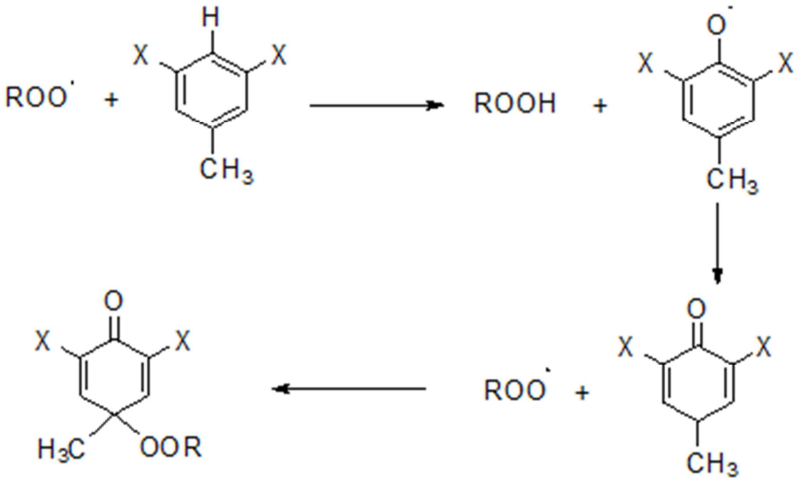
medicine has been formulated in 1985; at the beginning of 2015, approx. 138,000 PubMed entries show for this term. Oxidation is a free-radical chain process. Therefore, the most useful stabilizing agents will be those which combine with free radicals to give stable species incapable of further reaction. These stabilizing agents are called antioxidants. Antioxidants slow down the process of degradation so that the energetic action of the environment can lead to higher sustainability. They interact with free-radicals, making possible their reaction with oxygen[63].

3.1. Groups of Antioxidants

Antioxidants can be grouped into synthesis antioxidants and natural antioxidants. The difference between the two categories is that most synthesis antioxidants generate substances that develop cancer or other diseases. Antioxidants can be also classified, depending on their function or nature, into two large, basic groups: (i) Chain terminating or primary antioxidants; (ii) Hydroperoxide decomposers or secondary antioxidants, frequently called synegists[63].

3.1.1. Primary Antioxidants

They are strically hindered phenols or aromatic amines, capable of undergoing fat reaction with peroxy radicals and so are often called radical scavengers. This could be represented in Scheme 2.

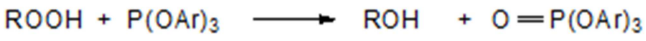


Scheme 2. *Action of primary antioxidants.*

The estrogens with phenolic structure possessed substantial activities with respect to the inhibition of lipid peroxidation (LPO). Concentrations of estradiol and estriol required to achieve 50% inhibition of membrane phospholipid peroxidation were about 4- to 6-times that of α-tocopherol, respectively[64].

3.1.2. Secondary Antioxidants

They are usually sulfur compounds or trimesters of phosphorous acid (phosphates). They have the ability to react with hydroperoxides to yield nonradical products, following heterocyclic mechanism. The reaction of phosphites to phosphates is an example (Eq. 1).



Eq. 1

3.2. How to Prevent Oxidation

There is no doubt that successful prevention is the key to controlling morbidity and mortality from chronic diseases affecting humankind. The possibility has arisen within the last three decades; those major diseases that directly affect humankind worldwide may be preventable by the simple improving of the dietary intake of the nutrient substances that have become called “antioxidant nutrients”.

The major role in antioxidant defense is fulfilled by antioxidant enzymes, not by small-molecule antioxidant compounds. Investigations of oxidative responses in different in vivo models suggest that, in complex organisms such as mammals, organs and tissues contain distinct antioxidant systems, and this may form the basis for differential susceptibility to environmental toxic agents. Thus, understanding the pathways leading to the induction of antioxidant responses will enable development of strategies to protect against oxidative damage[65].

The organism has several biological defense mechanisms against intracellular oxidative stress; including the enzymatic antioxidants such as superoxide dismutase, catalase, glutathione peroxidase and the non-enzymaticantioxidants such as glutathione, vitamins A, B, C and E, riboflavin[66].The redox signaling area of research is rapidly expanding, and future work will examine new pathways and clarify their importance in cellular pathophysiology.

Methods of prevention include: (i) Methods to avoid occurrence of disease and most population-based health promotion efforts are of this type; (ii) Methods to diagnose and treat extant disease in early stages before it causes significant morbidity; (iii) Methods to reduce negative impact of extant disease by restoring function and reducing disease-related complications; (iv) Methods to mitigate or

avoid results of excessive interventions in the health system.

3.3. Mode of Action

Free radicals and other reactive oxygen species (ROS) are constantly formed in the human body. Free-radical mechanisms have been implicated in the pathology of several human diseases, including cancer, atherosclerosis, malaria, rheumatoid arthritis, and neurodegenerative diseases. For example, the superoxide radical ($O^{2\cdot-}$) and hydrogen peroxide (H_2O_2) are known to be generated in the brain and nervous system in vivo, and several areas of the human brain are rich in iron, which appears to be easily mobilizable in a form that can stimulate free-radical reactions.

Antioxidant defenses to remove $O^{2\cdot-}$ and H_2O_2 exist. Superoxide dismutases (SOD) remove $O^{2\cdot-}$ by greatly accelerating its conversion to H_2O_2. Catalyses in peroxisomes convert H_2O_2 into water and O_2 and help to dispose of H_2O_2 generated by the action of the oxidase enzymes that are located in these organelles. Other important H_2O_2-removing enzymes in human cells are the glutathione peroxidases. When produced in excess, ROS can cause tissue injury. However, tissue injury can itself cause ROS generation (e.g., by causing activation of phagocytes or releasing transition metal ions from damaged cells), which may (or may not, depending on the situation) contribute to a worsening of the injury.

Imbalance in cell redox status resulting from excessive production of ROS and/or insufficient antioxidant capacity promotes both endothelial dysfunction and insulin resistance; therefore, restoring physiological redox balance is an attractive treatment approach[67].

Assessment of oxidative damage to biomolecules by means of emerging technologies based on products of oxidative damage to DNA (e.g., 8-hydroxydeoxyguanosine), lipids (e.g., isoprostanes), and proteins (altered amino acids) would not only advance our understanding of the underlying mechanisms but also facilitate supplementation and intervention studies designed and conducted to test antioxidant efficacy in human health and disease[68].

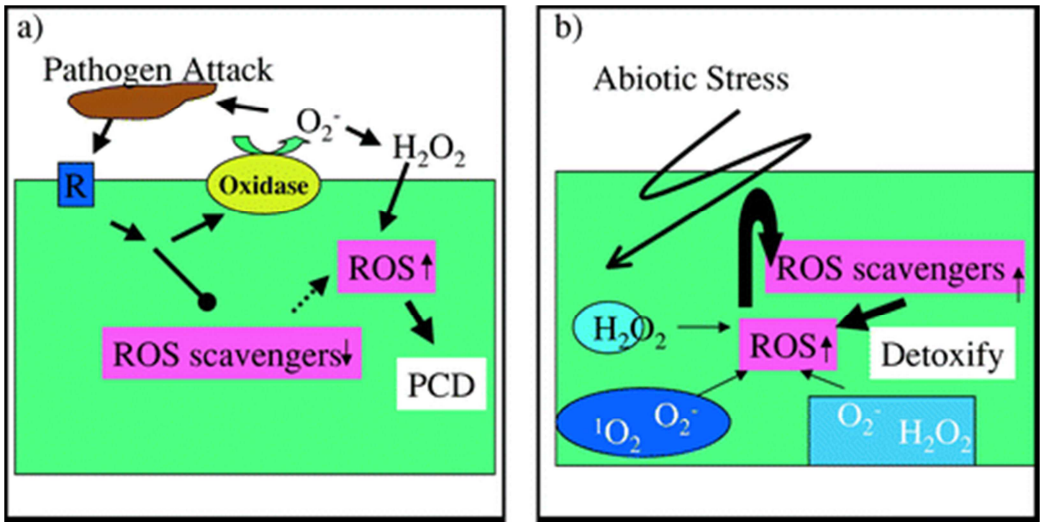


Fig 4. *Different roles of ROS under conditions of (a) pathogen attack or (b) abiotic stress (Apel, 2004)[69].*

In 2004, Apel, et. al[69]. reported that, ROS play a central role in plant pathogen defense (Figure 4a) and during abiotic stresses (Figure 4b). Upon pathogen attack, receptor-induced signaling activates plasma membrane or apoplast-localized oxidases that produce superoxide radicals ($O^{2\cdot-}$) that are highly toxic and can help to kill the invading pathogen. On the other hand, $O^{2\cdot-}$ is rapidly dismutated into hydrogen peroxide, which, in contrast to superoxide, can readily cross the plasma membrane. Intracellular ROS levels increase due not only to extracellular production of ROS but also by down-regulation of ROS scavenging mechanisms. Overall, ROS amounts increase to critical levels and induce programmed cell death (PCD). During abiotic stress, ROS production occurs mainly in chloroplasts and mitochondria at the sites of electron transport, increasing intracellular ROS amounts to toxic levels. The cellular response encompasses up-regulation of ROS scavenging mechanisms to detoxify increased amounts of ROS. However, the role that ROS play during abiotic stresses appears to be opposite to the role that ROS play during pathogen defense.

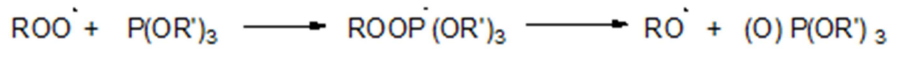
On the other hand, lipid peroxidation may be initiated by any species that possesses sufficient reactivity to abstract a hydrogen atom from a poly unsaturated fatty acid side chain in membrane lipids[70].

Organophosphorus compoundsand *P*-heterocycles in particular, have been recognized as antioxidant drugs [71,72]. Furthermore, their mechanism of action and the structure activity relationships (SAR) were extensively studied[73,74].

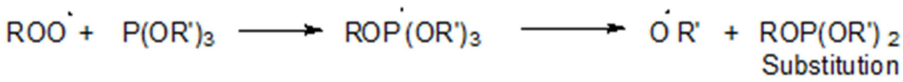
Depending on their structure and scavenging properties, phosphites and phosphonates may act as both primary and secondary antioxidants. In general, phosphites are considered to be hydroperoxide decomposing (secondary antioxidants), but certain aryl phosphites should also be capable of acting as radical chain-terminating (primary antioxidants) by trapping peroxyl radicals to give aroxyl radicals. The reaction modes and the relationship between structure, reaction mechanism,

and antioxidant activity has been elucidated[72,73].

Because phosphites first of all are oxidized by ROO· radicals to give phosphates and RO· radicals (Eq. 2), the further reaction of these alkoxyl radicals with the phosphorus compound is decisive. Only those phosphites (R'=Ar) which react with alkoxyl radicals by substitution to give an isomeric alkyl phosphite and chain terminating phenoxyl radicals (Eq. 3) can act as primary antioxidants[73,75-78].



Eq. 2



Eq. 3

Phosphites, phosphonites and other organic phosphorus compounds are used in organic polymers and other organic materials as antioxidants. In 1987, Lester et. al.[79] provided certain aromatic fluorophosphorus compounds which were proved to be very effective as stabilizers in a wide range of organic materials. This efficiency because they retard changes in viscosity of organic materials stabilized therewith for extensive periods of time under processing conditions. In addition, they are stable when stored at room temperatures. They are especially effective when used in combination with phenolic antioxidants.

In a previous study reported by Schwetlick, et. al.[80], it was proved that, in the autoxidation of hydrocarbons inhibited by aryl phosphites and phosphonites at 150–180°C, the phosphorus acid esters are hydrolysed to give phenols and hydrogen phosphites and phosphonites respectively. Under certain conditions, these hydrogen esters hydrolyze further to form phosphorous and phosphonic acid respectively. The mixture of antioxidants thus generated is responsible for the high stabilizing efficiency of phosphite and phosphonite esters in autoxidations at these temperatures.

Later on, Schwetlick, et. al.[81] studied the inhibition of the autoxidation of hydrocarbons by aliphatic, aromatic, sterically hindered, and cyclic phosphites by means of volumetric and ^{31}P-NMR techniques. The study indicated that, the antioxidant activity of phosphites depends on the rate of their reactions with peroxyl radicals and on the way they react with alkoxyl radicals. Generally, they are considered better than phenolic antioxidants at high temperatures as they eliminate hydroperoxides which decompose and lead to autoxidation chain reactions. Thus, phosphorus compounds are important for oxidative stability during various operations[81]. Water is always present in autoxidation at somewhat higher temperatures, especially in those inhibited by phosphorus compounds, resulting from dehydration of alcohols formed as in Eq. 1 and from thermal decomposition of hydroperoxides. It is well known too, that alkyl and non-hindered aryl phosphites and phosphonites easily hydrolyse at ambient temperatures. Hydrolysis of hindered aryl phosphites is more restrained, and does not occur under the conditions of autoxidation at low temperatures. At higher temperatures, however, it may become relevant. In addition to hydrolysis, oxidation of the phosphorus compounds by hydroperoxides and peroxyl radicals takes place in the course of the reaction giving the corresponding phosphates and phosphonates. The ratio of oxidation to hydrolysis depends on the oxidizability of the particular hydrocarbon and on the reaction conditions (temperature)[80].

3.4. Pharmacological Studies

In general, it is well established that pyrimidopyrimidines, analogues of folic acid (one of the B vitamins that is a key factor in the synthesis of nucleic acids RNA and DNA) and an important class of annulated uracil and thiouracil, are pharmacologically useful as powerful inhibitor of lipid peroxidation in human and rat liver [82,83]. The introduction of the phosphor moiety into these *N*-heterocycles has attracted much attention by many researchers in medicinal chemistry because this system of heterocycles was expected to enhance, the antioxidative properties[84].

Abdou, et. al.[84,85] demonstrated bioscreening of the antioxidant properties of selective synthesized phosphorus products. They were in vitro evaluated using Lipid Peroxidation (LPO) by two methods: 2,2`-Azobis-(2-amidino-propane)dihydrochloride (AAPH), and 2,2`-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS). Vitamin C is measured as a positive standard for the antioxidant activity in all experiments. The activity expresses their ability to inhibit LPO in rat's brain homogenate and the rate of erythrocyte hemolysis. Pro-oxidant activities of the synthesized products were also assayed for their effect on bleomycin-induced DNA damage. The antioxidant evaluation revealed that the thiazolophosphonate derivatives exhibited a higher antioxidant activity than that of their fused pyrrolopyrimidinonephosphonate counterparts. Nevertheless, the diphosphonates manifested the best protective effects against DNA damage induced by bleomycin[84].

Results also showed the ability of the synthesized benzothiazaphosphepines and relevant phosphonates to inhibit LPO in rat's brain homogenate and the rate of erythrocyte hemolysis[85]. Nonetheless, it seems reasonable to assume that some of these researches will be translated into new indications for phosphorus compounds use as antioxidative agents.

4. Phosphorus Compounds as Antidiabetics

Diabetes mellitus II is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin action in tissues (insulin resistance) and/or defects in pancreatic insulin secretion (β-cell dysfunction), which

eventually includes loss of pancreatic insulin-secreting cells[86,87].

In 2001, Zimmet, et.al.[88] expected that, the number of people with diabetes would double to ~300 million within 20 years. The associated complications of diabetes, such as cardiovascular disease, peripheral vascular disease, stroke, diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy (eventually blindness) result in increasing disability, reduced life expectancy, and enormous health costs.

4.1. Pharmacological Studies

In patients with type 2 diabetes, the pancreatic and hepatic glucokinase activity, as well as the pancreatic glucokinase mRNA, is reduced by at least 50%. However, the exact glucokinase status of individual patients is not known and is not used as an indicator of the individual stage of the disease[89]. Glucokinase mutations may be related to maturity onset of diabetes of the permanent neonatal diabetes mellitus[90,91]. Altogether, a broad range of "glucokinase diseases" exist, with close to 250 known missense and nonsense mutations, as well as insertions, deletions, and splice variants[92].

The established drugs [sulfonylureas, glinides, glucagon-like peptide 1 (GLP-1) receptor agonists, metformin, thiazolidinediones, and α-glucosidase inhibitors] generally target insulin resistance or β-cell dysfunction by increasing insulin secretion or tissue sensitivity to insulin[93].

Drugs addressing other aspects of the disease including promising emerging biological/molecular targets are still under investigation. Many compounds are derived from physiological compounds (hormones) aiming at improving their kinetics and selectivity, and others are chemical compounds that were obtained by screening for a newly identified target in the physiological or pathophysiological machinery. Many unsolved problems exist including: a) Reduced β-cell sensitivity to glucose ("sensor defect"); b) Loss of β-cell number/function (no halting of diabetes progression); c) Loss of oscillations of insulin secretion; d) Loss of first-phase insulin response to a glucose challenge; e) Elevated pro-insulin/insulin ratio; f) Abnormally high secretion of amylin; g) Increased glucagon secretion (gluconeogenesis, glucose production).

In addition, many marketed drugs have major drawbacks that hamper therapy, and modifications in dosing and/or new compounds should be developed to overcome these issues[94]. Among others, the following problems continue to plague current therapy: a) Hypoglycemias (especially when initiating therapy; severe hypoglycemias are known to lead to myocardial infarction and to the development of dementias); b) Many of these pathophysiological parameters are linked to more than one secondary complication, such as increased vascular permeability, alterations in blood flow, and stimulation of neovascularization[95]; c) Weight gain (a leading factor driving the epidemic of diabetes); d) Increase in insulin resistance; e) β-Cell destruction.

4.2. Recent Trends in Therapy

Hyperglycemia induces various diabetic complications via different mechanisms, which are the basis for therapies. Since many defects overlap between various complications, they are first solely listed and afterward the remedies are described.

Current therapies for type 2 diabetes mellitus have mainly centered on elevating plasma insulin levels (direct insulin administration or oral agents that promote insulin secretion), improving insulin sensitivity of tissues, and eventually reducing the rate of carbohydrate absorption from the gastrointestinal tract[95].

This review article spots two of the most attractive recent trends in therapies for type 2 diabetes[96-109]. The first trend is a new perspective, even a paradigm change, which has recently been brought forward by a new class called incretin enhancers[96-100].

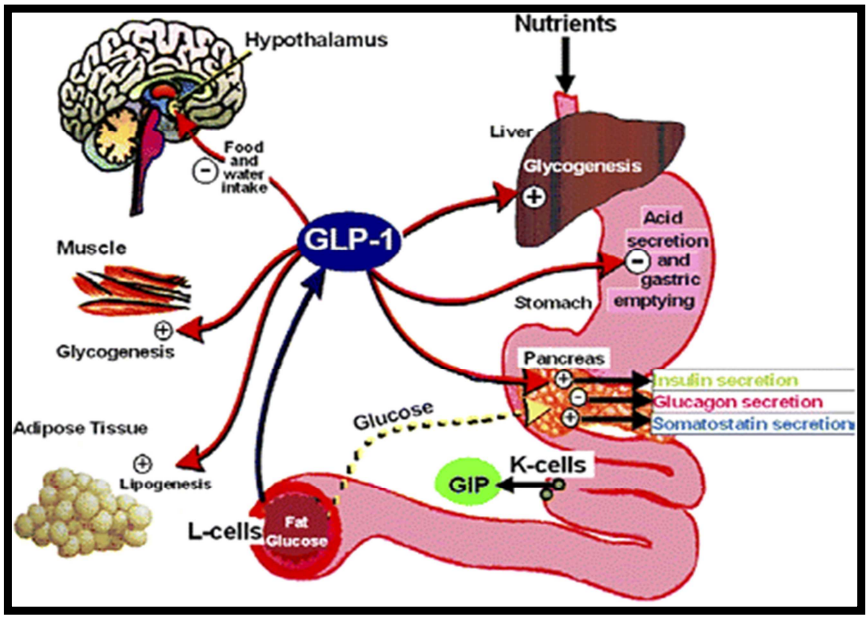


Fig 5. *Summary of effects of GLP-1 (Verspohl, 2009)[97].*

Incretins are defined as being responsible for a higher insulin response to oral intake of glucose compared with an equal intravenous glucose load (i.e., reaching equivalent plasma glucose levels)[96]. GLP-1 receptor function and subsequent signaling has been demonstrated in recent litreatures[97-100] (Fig. 5). Albiglutide improves glycemic control across a variety of doses and dosing schedules, Albiglutide mimics the full range of GLP-1 actions, second messengers, and mechanisms[99].

The clinical properties of the GLP-1 receptor agonist albiglutide (phase III; structural details in Fig. 6) have been reviewed[99,100]. On March 2014, GLP-1 receptor agonist albiglutide (GLP-1RAs) has been established as an important total treatment strategy for patients with type 2 diabetes who do not tolerate metformin[99]. It is approved as add-on therapy in combination with other blood-glucose lowering drugs including insulin when these, together with diet and exercise, do not provide adequate glycaemic control. Albiglutide is injected under the skin once a week with a single use pen injector[100]. Its long plasma half-life of 5 days (improved pharmacokinetics) enables once-weekly dosing, as a result of covalent binding of albumin. The tandem repeat structure (Fig. 6) improves the potency observed when only one GLP-1 moiety was covalently linked to albumin (note: a bulky carrier molecule)[98].

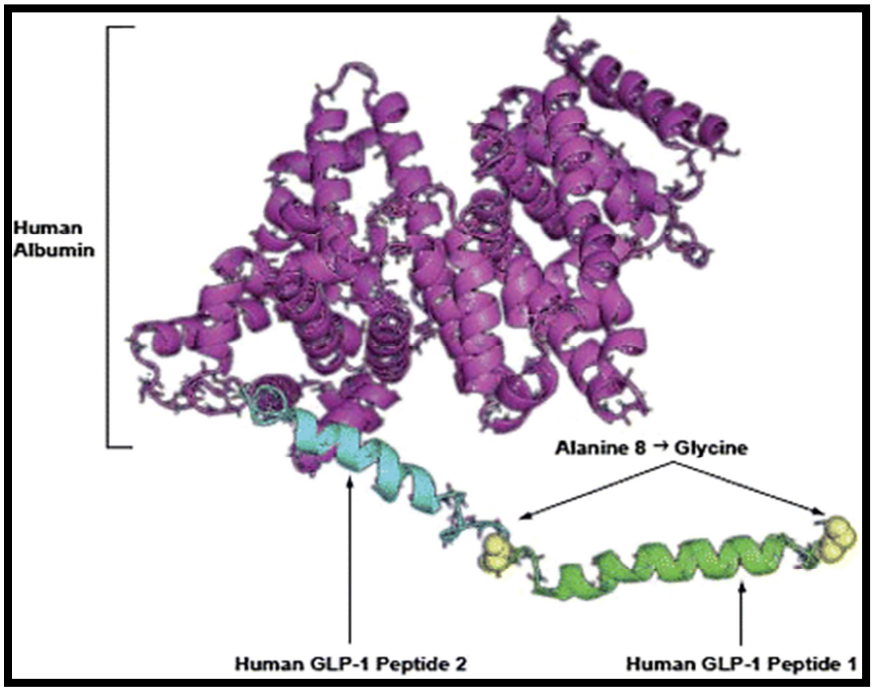


Fig 6. *Theoretical structure of albiglutide (Rosenstock, 2009)[98].*

The second trend is the development of glucokinase activators has a long history[101,102]. Pancreatic β cells and the liver play key roles in blood glucose homeostasis[103]. In both organs, glucose is transported into the cell by the low-affinity glucose transporter GLUT2. Rate-limiting phosphorylation of glucose by glucokinase is the first step initiating glycogen synthesis in the liver[104] and insulin release in β cells[102]. Glucokinase - also known as hexokinase IV, hexokinase D (ATP: d-glucose 6-phosphotransferase; EC 2.7.1.2), or d-glucose- phosphorylates other hexoses, such as d-fructose, d-mannose, or 2-deoxy-d-glucose by ATP according to the following equation (Eq. 4):

$$RCH_2OH + MgATP^{2-} \longrightarrow RCH_2{-}OPO_3^{2-} + MgADP^{-} + H^{+} \quad \text{Eq. 4}$$

Glucokinase has a higher Km (6–10 mM) for glucose than the other hexokinases, which are saturated at this concentration. Therefore, only glucokinase activity correlates with physiological rises of blood glucose concentrations from fasting (5 mM) to postprandial (10–15 mM) levels. This is why glucokinase is often referred to being a "glucose sensor" in β cell[105] and the "glucostat" concept was developed[106]. As a sensor, it determines the rate and threshold concentration of glucose (~5 mM) required to initiate the signaling cascade leading to insulin release[107]. In Fig. 7, various roles of glucokinase are summarized, including those for β cells and liver.

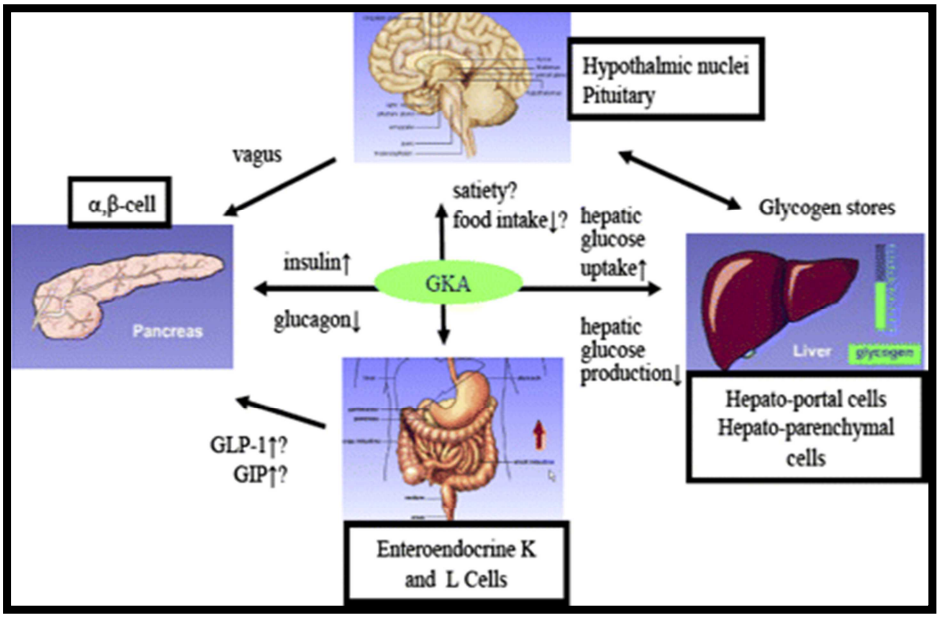


Fig 7. *Role of glucokinase in various tissues (Verspohl, 2012)*[106].

Sarabu, et. al.[108,109] described a pharmacophore model of the heterogeneous chemical group of most known classes of glucokinase activators. The key structural features common to both single atom-centered (carbon or nitrogen) and aromatic ring-centered glucokinase activators, including three attachments, two of which are hydrophobic groups (with at least one consisting of an aromatic ring structure) and the other contributes a hydrogen bond donor-acceptor pair. The establishment of a crystal structure of recombinant human glucokinase was mainly put forward by the availability of glucokinase activators[110]. For the allosteric activator site, as many as nine contact amino acids, depending on the chemistry of the drug, have been identified, encompassing Val62, Arg63, Glu210, Ile211, Tyr214, Tyr215, Met235, Val452, and Val455. The link between enzyme kinetic and structure-activity relationship (SAR) has not yet been sufficiently investigated[101,110,111].

Increased superoxide anion production induced by hyperglycemia leads to decreased activity of glycerinaldehyde-3-phosphate dehydrogenase and to consequential increased activity of alternative pathways, including the polyol, hexosamine, diacylglycerol, PKC, and AGE pathways. Glucose pathways during hyperglycemia resulting mainly in cell dysfunctions. Excessive glucose metabolism generates NADH and overload of the electron transport chain, causing oxidative stress. Finally, many pathways are activated, leading to inflammation and neuronal dysfunction[112-114] (Fig. 8).

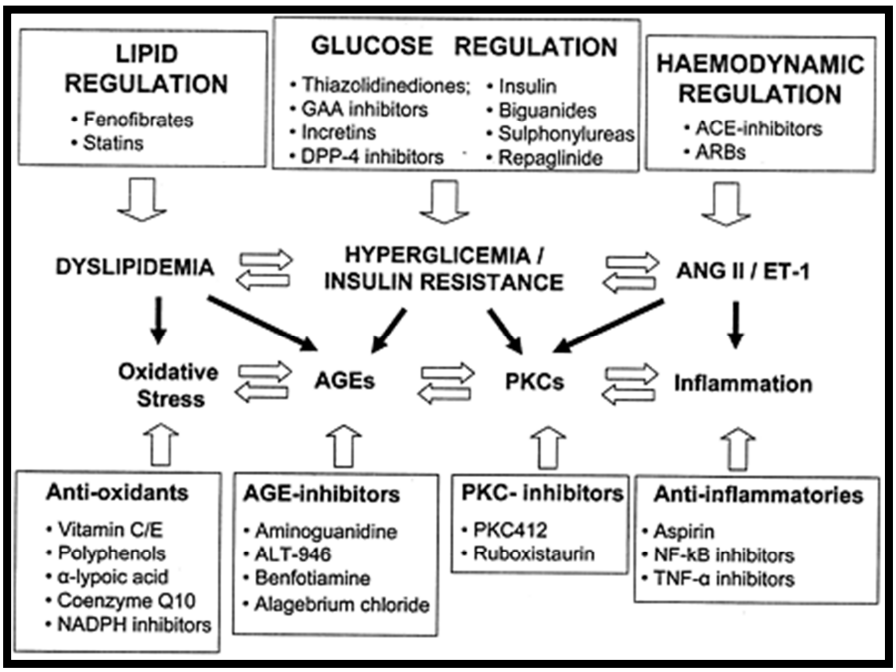


Fig 8. *Pathophysiological factors (Conway, 2009)*[113].

Some methods to mitigate or avoid diabetic complications include: a) Inhibition of increased glucose flux through the polyol pathway (aldose reductase inhibition); b) Inhibition of increased formation of advanced glycation end-products (AGE); c) Inhibition of protein kinase C (PKC) isoforms; d) Inhibition of increased hexosamine biosynthesis pathway; e) Inhibition of reactive oxygen species (ROS) and superoxide formation; f) Inhibition of the transforming growth factor-β (TGF-β) secretion; g) Activation of transketolase, and inhibition of poly(ADP-ribose) polymerase (PARP).

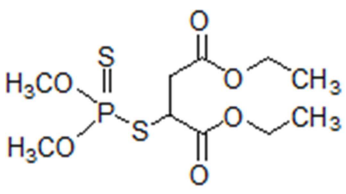
Normal physiological functions such as gastric emptying (slowing) or renal glucose re-absorption (blocking to increase glucose loss) could also be potential targets for future therapies. One possibility is the comprehensive gene expression analyses of critical tissues for understanding the molecular signature of type 2 diabetes. Serial analysis of gene expression techniques has made it possible to compare tag levels among independent libraries and to identify previously unrecognized genes with novel functions that may be important in the development of diseases. Such serial analysis of gene expression-based approaches may lead to the identification of novel therapeutic targets for the treatment of type 2 diabetes and its complications.

In some areas, great progress is observed (e.g., incretin area) [96-100]; in others, no great progress is obvious (e.g., glucokinase activators) [101-109], and other areas are not recommended for further research.

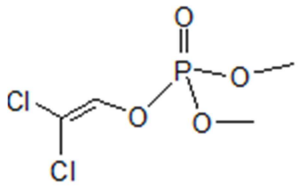
4.3. Uses of Organophosphorus Compounds as Antidiabetics

Several drugs such as metformin, biguanides/ metformin (Glucovance), sulfonylureas/ metformin (glibenclamide), and others are presently available to reduce hyperglycemia in diabetes mellitus. Despite their wide spread use, none of the presently available agents is ideal; each has its shortcoming and side effects[115]. Thus, the continuous search for novel antidiabetic agents that are more effective and safe is a target of research by many investigators.

Heterocyclic phosphor esters are known to serve as both hyperglycemic and hypoglycemic agents in different concentrations[115-118], e.g., diisopropylphosphorofluoridate has the activity to reduce the glucose level (hypoglycemia)[116]. In addition, studies on the effect of organophosphorus compounds (OPC) on carbohydrate metabolism showed an increase in blood glucose in various constituents of brain rats after treatment with malathion[117] (Structure 1). Nevertheless, glycogen levels were decreased in rat liver when treated with dichlorovos[118] (Structure 2).



Structure 1. *Malathion (Al-Ghanim, 2012)[117].*



Structure 2*. Dichlorovos (Lakshmanan, 2013)[118].*

Recentely, Abdou, et. al.[84,85] have evaluated the antidiabetic activity of selective synthesized substituted bicyclic 6,6- and 6,5- membered phosphonates, the results were presented while % potency of the tested phosphonates*vs* blood glucose levels of diabetic rats was displayed, and glibenclamide was used as a reference standard. The tested phosphonates have shown hypoglycemia effectthat can decrease the blood glucose levels in diabetic rats. The screening for the antidiabetic effect of the tested products was carried out in ethanolic solution on streptozotocin-induced diabetic rat in duration dependent fashion. Streptozotocin injection induced diabetes mellitus, which may be due to destruction of *β*-cells of Islets of Langerhans as proposed by others[119]. After 7 days and 14 days supplementation of ethanol solutions of the tested compounds resulted in significant diminution of fasting blood glucose level in respect to diabetic rat, but no significant alteration of fasting blood glucose level to the control, which further strengthens the antidiabetogenic action of these compounds. Fasting blood glucose level of all animals before treatment was within the normal range then it was significantly elevated after 24 h of streptozotocin injection with respect to the control level. The screening results showed that the tested phosphonates exhibit a potent to moderate effects on diabetes mellitus II, suggesting new generation of antidiabetogenic drugs[84,85]. At the time being, there has been a return to laboratory studies that are helping to solve how these OPC can work at a cellular level. As a result, their full therapeutic potential is gradually being realized. The journey, as usual started with chemistry, which led to laboratory studies related to the mechanism of action of such OPC as antidiabetic agents.

5. Conclusion and Prospective

In summary, the discovery and development of phosphorus compounds as a major class of drugs for treatment of many diseases has been a fascinating saga that is not yet completed.

The introduction of bisphosphonates in oncology has dramatically changed the management of patients with metastatic bone disease. Particularly remarkable is their anticancer activity. In contrast, many studies proved that aminophosphonates exhibited promising antimicrobial, antioxidant, and anticancer activity.

Many phosphorus compounds are proved to be important agents for oxidative stability during various operations. Phosphites and phosphonates may act as both primary and secondary antioxidants. Results showed the ability of many phosphonates to inhibit LPO and the rate of erythrocyte

hemolysis in rat's brain homogenate. Consequently, the potential benefits of phosphorus compounds as antioxidative agents are needed to be considered.

On the other hand, and regarding to type 2 diabetes mellitus, none of the presently available drugs to reduce hyperglycemia is ideal. Thus, the continuous search for novel, more effective and safe antidiabetic agents -that may involve OPC- is a target of future research. Despite the synthesis of hundreds of compounds, no clear-cut structure-effect relationship has been unraveled up to now.

References

[1] Mader, M. M., Bartlett P. A., *Chem. Rev.,* 1997, 97, 1281-1301.

[2] Holla, B. S., Ashok, M., *Phosphorus, Sulfur, Silicon, and Relat. Elem.* 2007,182, 981-991.

[3] Bul, E. O. J., Naidu, M. S. R., *Phosphorus, Sulfur, Silicon, and Relat. Elem.,* 2000,162, 231-243.

[4] Gilard, V., Martino, R., Malet-Martino, M., Niemeyer, U., Pohl, J., *J. Med. Chem.,* 1999, 42, 2542-2560.

[5] Maier, L., Diel, P. J., *Phosphorous Sulphur and Silicon*, 1991, 57, 57-64.

[6] Leon, A., Liu, L., Yang, Y., Hudock, M. P., Hall, P., Yin, F., Studer, D., Puan, K. J., Morita, C. T., Oldfield, E., *J. Med. Chem*., 2006, 49, 7331-7341.

[7] Kafarski, P., Lejczak, B., *Curr. Med. Chem. Anticancer Agents*, 2001, 1, 301-312.

[8] Gouverneur, V., Lalloz, M. N., *Tetrahedron Lett.,* 1996, 37, 6331-6334.

[9] Yoneda, T., Sasaki, A., Dustan, C., William, P. J., Bauss, F., De Clerck, Y. A., Mundy, G. R., *J. Clin. Invest*., 1997, 99, 2509-2517.

[10] Ross, J. R., Saunders, Y., Edmonds, P. M., *BMJ*, 2003, 327, 469-474.

[11] Tim, V. W., Manon, T. H., Eric, F., Jan, B. V., *The Oncologist,* 2009, 14, 181-191.

[12] Sanders, J. M., Ghosh, S., Chan, J. M., Meints, G., Wang, H., Raker, A., *J. Med Chem.,* 2004, 47, 375-384.

[13] Thompson, K., Rogers, M. J., *J. Bone Miner Res.*, 2004, 19, 278-288.

[14] Graham, R., Russell, G., *Bone*, 2011, 49, 2-19.

[15] Waldmann, H., Bialy, L., *Angew. Chem.,* 2005, 44, 3814-3819.

[16] Gautier, A., Garipova, G., Salcedo, C., Balieu, S., Piettre, S. R., *Angew. Chem. Int. Ed.,* 2004, 43, 5963-5967.

[17] Drake, M. T., Cremers, S. C., *Mol. Interv*., 2010, 10,141-152.

[18] Martin, T. J., Grill, V., *Australian Prescriber,* 2000, 23, 130-132.

[19] Fernandes, C., Leite, R., Rodrigo, S., Lancas, F. M., *Quimica Nova*, 2005, 28, 274-280, *Chem. Abstr*. 2005, *142*, 366626.

[20] Papapoulos, S. E., *Nature Reviews Rheumatology*, 2013, 9, 263-264.

[21] Boikos, S. A., Hammers, H. J., *Journal of Clinical Oncology (JCO)*, 2012, 30, e299.

[22] Saunders, Y., *Palliat Med*., 2004, 18, 418-431.

[23] Hung, S. H., Tsai, W. Y., Tsao, P. N., Chou, H. C., Hsieh, W. S., *Journal of the Formosan Medical Association*, 2003, 102, 801-804.

[24] Graham R., Russell G., *Bone*, 2011, 49, 2-19.

[25] McClung M. R., *J. Clin. Densitom.*, 2010, 13, 132.

[26] Reid I. R., Brown J. P., Burckhardt P., Horowitz Z., Richardson P., Trechsel U. N., *Engl. J. Med.*, 2002, 346, 653-661

[27] van-Beek, E., Löwik, C., van der Pluijm, G., Papapoulos, S., *J. Bone Miner. Res.*, 1999, 14, 722–729.

[28] Clézardin, P., Ebetino, F. H., Fournier, P. G., *Cancer Res.*, 2005, 65, 4971-4974.

[29] Abdou, W. M., Ganoub, N. A., Fahmy, A. F. M., Shaddy, A. A., *Monatsh. Chem*. 2006, 136, 105-116.

[30] Abdou, W. M., Khidre, R. E., Kamel, A. A., *Arch. Pharm. Chem. Life Sci.,* 2012, 345, 123-136.

[31] Abdou, W. M., Khidre, M. D., Sediek, A. A., *The design and synthesis of sulfur and nitrogen containing bisphosphonic acids and their role in oncology in: The chemistry and biologically activity of synthetic and natural compounds, modern aspects of chemistry of heterocycles,Russian Academy of Natural Science*, Kartsev, V. G. (ed.).2010, pp. 209-212.

[32] Abdou, W. M., Shaddy, A. A., *J. Med. Chem. Res*., 2010, 19, 39-40.

[33] Abdou, W. M., Khidre, R. E., Shaddy, A. A., *J. Heterocyclic Chem.*, 2013, 50, 33-41.

[34] Abdou, W. M., Kamel, A. A., Shaddy, A. A., *Eur. J. Med. Chem*., 2010, 45, 5217-5224.

[35] Abdou, W. M., Shaddy, A. A., *Arkivoc,* 2009, 14,143-182.

[36] Abdou, W. M., Ganoub, N. A., EL-Khoshnieh, Y. O., *Synlett*, 2003, 785-790.

[37] Prasad, G. S., Rao, G. N., *Journal of Modern Medicinal Chemistry,* 2013, 1, 49-60.

[38] Moonen, K., Laureyn, I., Stevens, C. V., *Chem Rev*, 2004, 104, 6177-6185

[39] Laureyn, I., Stevens, C. V., Soroka, M., Malyse, P., *Arkivoc*, 2003, 6, 102-115.

[40] Kafarski, P., Lejczak, B., *Current Medicinal Chemistry - Anti-Cancer Agents*, 2001, 1, 301-312.

[41] Abdel-Monem, W. R., *Eur. J. Chem*., 2010, 1, 168-172.

[42] Schug, K. A., Lindner, W., *Chem. Rev.* 2005, 105, 67-114.

[43] Wrobleski, S. T., Lin, S., Hynes, J. Jr., Wu, H., Pitt, S., *Bioorg. Med. Chem. Lett.,* 2008, 18, 2739-2744.

[44] Prasad, G. S., Rao, G. N., *Journal of Modern Medicinal Chemistry,* 2013, *1,* 49-60.

[45] Chandrasekhar, S., Narsihmulu, Ch., Shameen, S. S., Saritha, B., Jayaprakash, S., *Synlett,* 2003, 505-506.

[46] Takahashi, H., Yoshioka, M., Imai, N., Onimura, K., Kobayashi, S., *Synthesis,* 1994, 8, 763-764.

[47] Heydari, A., Karimian, A., Ipaktschi, J., *Tetrahedron Lett,* 1998, 39, 6729-6732.

[48] Azizi, N., Saidi, M. R. *Eur. J. Org. Chem.,* 2003, 46, 30-33.

[49] Lee S., Park J. H., Kang J, Lee J. K., *J., Chem.Soc. Chem.Commun*., 2001, 1698-1699.

[50] Akiyama, T., Sanada, M., Fuchibe, K., *Synlett,* 2003, 1463-1464.

[51] Abdou, W. M., Barghash, R. F., Bekhiet, M. S., *RSC Org. Advances,* 2013, 1528-1540.

[52] Shaddy, A. A., Kamel, A. A., Abdou, W. M., *Synth. Commun*., 2013, 43, 236-252.

[53] Abdou, W. M., Barghash, R. F., Sediek, A. A., *Eur. J. Med. Chem*., 2012, 57, 362-372.

[54] Abdou, W. M., Barghash, R. F., Bekheit, M. S., *Arch. Pharm. Chem. Life Sci.* 2012, 345, 884-895.

[55] Kamel, A. A., Geronikaki, A., Abdou, W. M., *Eur. J. Med. Chem*. 2012, 51*,* 239-249

[56] Abdou, W. M., Kamel, A. A., Khidre, R. E., Geronikaki, A., Ekonomopoulou, M. T., *Chem. Biol. & Drug Des.,* 2012*,* 79, 719-730.

[57] Abdou, W. M., Barghash, R. F., Khidre, R. E., *Monatsh. Chem*., 2013, 144, 1233-1242.

[58] Hirschmann, R., Smidt, A. B., Taylor, C. M., Benkovic, P. A., Taylor, S. D., Yager, K. M., Sprengeler, P. A., Benkovic, S. J., *Science*, 1994, 265, 234-237.

[59] Meyer, F., Laaziri, A., Papini, A. M., Uziel, J., Juge, S., *Tetrahedron,* 2004, 60, 3593-3597.

[60] Smith, W. W., Bartlett, P. A., *J. Am. Chem. Soc.,* 1998, 120, 4622-4628.

[61] For examples and applications of different naturally occurring *β*-aminophophonates/ phosphonic acids see, e.g.: *Aminophosphonic and aminophosphinic acids, chemistry and biological activity*, ed. V. P. Kukhar, H. R. Hudson, John Wiley and Sons, NY, 2000.

[62] He, X. P., Xie, J., Tang, Y., Li, J., Chen, G. R., *Curr. Med. Chem*., 2012, 19, 2399-2405.

[63] Butnariu, M., Grozea, I., *J. Bioequiv. Availab.*, 2012, 4, xvii-xix.

[64] Sugioka, K., Shimosegawa, Y., Nakano, M., *FEBS Letters*, 1987, 210, 37-90.

[65] Pacheco, J., Gonsebatt, M., *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, 2009, 674, 137–147.

[66] Evans, P., Halliwell, B., *British Journal of Nutrition*, 2001, 85, 67S-74S.

[67] Potenza, N., Papa, U., Russo, A., *Cell Biol. Int.*, 2009, 33, 734-738.

[68] Aruoma, O. I., *Journal of the American Oil Chemists' Society*, 1998, 75, 199-212.

[69] Apel, K., Hir, H., *Annual Review of Plant Biology*, 2004, 55, 373-399.

[70] Catalá, A., *The International Journal of Biochemistry & Cell Biology*, 2006, 38, 1482–1495.

[71] Nurulain, S. M., Szegi, P., Tekes, K., *Naqvi S. N.*, 2013, 64, 169-177.

[72] Schwetlick, K., Pionteck, J., Habicher, T. W. D., *Eur. Polymer J.* 1987, *23*, 383-388.

[73] Földes, E., Maloschik, E.,Kriston, I., Staniek, P., Pukánszky, B., *Polymer Degradation and Stability,* 2006, 91,479–487.

[74] Schwetlick, K., *In mechanism of polymer of degradation and stabillisation,* ed. Elsevier Applied Science, London and New York, 1990.

[75] Hall, G. H., Neal, M. A., Jenkins, S. D., Siddiqui, J. A., *US6827897 B2,* 2004, US 09/818,334.

[76] Vulic, I.,Vitarelli,G.,Zenner, J. M., *Polymer Degradation and Stability,* 2002,78, 27–34.

[77] Schwetlick, K., Habicher, W. D., *Die Angewandte Makromolekulare Chemie*, 1995, 232, 239–246.

[78] Habiche, W. D., Bauer, I., Pospíšil, J., *Macromolecular* Symposia, 2005, 225, 147–164.

[79] Lester, P. J., Burton, *US 4912155 A*, 1987.

[80] Schwetlick, K., König, T., Rüger, C.,Pionteck, J., Habicher, W. D., *Polymer Degradation and Stability,* 1986, 15, 97–108.

[81] Schwetlick, K., Pionteck, J., Winkler, A., Hfihner, U., Kroschwitz, H., Habicher, W. D., *Polymer Degradation and Stability*, 1991, 31, 219-228.

[82] Ahmed, O. M., Hussein, A. M., Ahmed, R. R., *Med.Chem.,* 2012, 2, 20-28.

[83] De la Cruz, J. P., Carrasco, T., Ortega, G., Sanchez, C. F.*, Lipids*, 1992, 27, 192-194.

[84] Kamel, A. A., Khidre, M. D., Abdou, W. M., *Heterocyclic Chemistry*, accepted for publications, 2014, DOI 1002/jhet.2260, Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).

[85] Abdou, W. M., Ganoub, N. A., Barghash, R. F., *Synthetic Communications*, 2014, 44, 2669-2678.

[86] Rosenbloom, A. L., Joe, J. R., Young, R. S., Winter, W. E., *Diabetes Care,* 1999, 22, 345-354.

[87] Kamaeswara, B. R., Giri, R., Kesavulu, M. M., Apparao, C. H, *J. Ethnopharmacol*., 2001, 74, 69-74.

[88] Zimmet, P., Alberti, K. G., Shaw, J., *Nature*, 2001, 414, 782-787.

[89] Caro, J. F., Triester, S., Patel, V. K., Tapscott, E. B., Frazier, N. L., Dohm, G. L., *Hormone and Metabolic Research,* 1995, 27, 19-22.

[90] Stride, A., Shields, B., Gill-Carey, O., Chakera, A. J., Colclough, K., Ellard, S., Hattersley, A. T., *Diabetologia*, 2014, 57, 54-56.

[91] Gloyn, A. L., *Hum. Mutat*., 2003, 22, 353-362.

[92] Gloyn, A. L., *Front diabetes, in Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics,* Matschinsky, F. M., Magnuson, M. A. (eds.), 16, pp 92-109, Karger, Basel, 2004.

[93] Abdul-Ghani, M. A., DeFronzo, R. A., *Endocr. Pract.,* 2008, 14, 782-790.

[94] Agius, L., *Biochem*., 2008,414, 1-18.

[95] Takagi C, Bursell S. E., Lin Y. W., Takagi H., Duh E., Jiang Z., Clermont A. C., King G. L*., Invest. Ophthalmol. Vis. Sci.*, 1996*,* 37, 2504-2518.

[96] Deacon, C. F., Carr, R. D., Holst, J. J., *Frontiers in Bioscience*, 2008, 13, 1780-1794.

[97] Verspohl E. J., *Pharmacol. Ther.,* 2009, 124, 113-138.

[98] Rosenstock, J., Reusch, J., Bush, M., Yang, F., Stewart, M., *Diabetes Care,* 2009, 32, 1880- 1886.

[99] Trujillo, J. M., Nuffer, W., *Ann Pharmacother*., 2014, 48, 1494-1501.

[100] Yabe, D. , Kuwata, H., Usui, R. , Kurose, T. , and Seino, Y., *Current Medical Research & Opinion*. *Informa Healthcare*, Posted online on May 20, 2015 (doi:1185/030079201045471).

[101] Priyadarsini, R. L., Namratha, J. R., Reddy, D. R., *International Journal of Pharmacy and Pharmaceutical Sciences*, 2012, 4, 81-87.

[102] Pal, M., *Curr. Med. Chem*., 2009, 16, 3858-3874.

[103] Bae, J., Kim, T., Kim M., Park, J., Ahn, Y., *Sensors*, 2010, 10, 5031-5053.

[104] Matschinsky, F. M., *Nat. Rev. Drug Discov.*, 2009, 8*,* 399-416.

[105] Matschinsky, F. M., *Diabetes*, 2002, 51, S394-S404.

[106] Verspohl, E. J., *Pharmacological Reviews*, 2012, 64, 188-237.

[107] Grimsby, J., Matschinsky, F. M., Grippo, J. F., *Discovery and actions of glucokinase activators, in Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics,* Matschinksy, F. M., Magnuson, M. A. (eds), 16, pp 360-378, Karger, Basel, 2004.

[108] Sarabu, R., Berthel, S. J., Kester, R. F., Tilley, J. W., *Expert Opin. Ther. Pat*, 2008, 18, 759-768.

[109] Grimsby, J., Berthel, S. J., Sarabu, R., *Curr. Top. Med. Chem.,* 2008, 8, 1524-1532.

[110] Dunten, P., Swain, A., Kammlot, U., Crowther, R., Lukacs, C. M., Levin, W., Reik, L., Grimsby, J., Corbett, W. L., Magnuson, M. A., Matschinsky, F. M., Grippo, J. F., *Crystal structure of human liver glucokinase bound to a small molecule allosteric activator. Insights into the activating mutations, in Glucokinase and Glycemic Disease: From Basics to Novel Therapeutics Front Diabetes,* Matschinsky, F. M., Magnuson, M. A. (eds.), 16, pp 145-154, Karger, Basel, 2004.

[111] Kamata, K., Mitsuya, M., Nishimura, T., Eiki, J., Nagata, Y., *Structure,* 2004, 12, 429-438.

[112] Gnudi, L., Gruden, G., Viberti, G*., Pathogenesis of diabetic nephropathy, in Textbook of Diabetes*, Pickup, J. C., Williams, G. (eds.), pp 1-21, Blackwell Science, Oxford, 2003.

[113] Conway, B. R., Maxwell, A. P., *Nephron.,* 2009, 112, 213-221.

[114] Obrosova, I. G., *Neurotherapeutics,* 2009, *6*, 638-647.

[115] Shu, Y., Sheardown, S. A., Brown, C., Owen, R. P., Zhang, S., Castro, R. A., Ianculescu, A. G., Yue, L., Lo, J. C., Burchard, E. G., Brett, C. M., Giacomini, K. M. J., Clin. Invest. 2007, 117, 1422-1431.

[116] Chatterjee, A. K., Kaveeshwar, U., *Defence Science Journal*, 1991, 41, 143-147.

[117] Al-Ghanim, K. A., *Scientific Research and Essays*, 2012, 7, 1674-1680.

[118] Lakshmanan, S., Rajendran, A., Sivasubramaniyan, C., *International Journal of Research in Biological Sciences*, 2013, 3, 34-38.

[119] Kavalali, G. H., Tuncel, S., Goksel, H. H., Hatemi, J., *Ethnopharmacol*., 2002, 84, 241-245.