

José R. Pérez-Castiñeira

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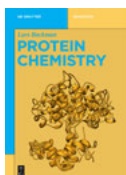


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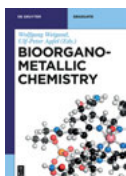


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José R. Pérez-Castiñeira

# Chemistry and Biochemistry of Food

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DE GRUYTER

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*Dedicado a Isabel, Manuel y Santiago*  
*Gracias por vuestro amor, paciencia y comprensión*



## Preface

In December 2017, I received an email from De Gruyter offering me the opportunity to write a book about chemistry and biochemistry of food, a subject that I had been teaching at the Faculty of Chemistry of the University of Sevilla for 17 years at that time. After a period of hesitation, I was persuaded by my wife, Isabel, to seize this opportunity; therefore, I took up the task of writing a book that aimed at graduate students of chemistry, biology, biochemistry, and similar areas of study, as well as undergraduate students with an adequate chemical background. During its writing, the book has not only grown beyond my initial plans but has also taught me much about science and about myself. I hope that this effort will help readers to learn and understand a bit more about the scientific bases of foods and nutrition. Science is an ever-changing process and I have tried to reflect that along the book, knowing that many of its contents will be amended, discarded, and/or extended in the future, because this is at the core of the scientific method.

I express my acknowledgment to a number of people who have helped me. First, I am most grateful to colleagues who agreed to write some of the chapters: Dr. José María Vega Piqueres, Emeritus Professor of Biochemistry at the University of Sevilla; Dr. Javier Vigara Fernández, Associate Professor of Biochemistry at the University of Huelva; Dr. María Montaña Durán-Barrantes, Associate Professor of Chemical Engineering at the University of Sevilla; and Dr. Victoria Valls-Bellés, Associate Professor of Physiology at the University Jaume I of Castellón de la Plana.

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I hope that my students have learned at least something about the chemistry of life in my lectures as well as in the final year projects and master’s and doctoral theses I have supervised. I can say that I have also learned a lot from them along the years and hope to learn more in the future. This book is also dedicated to them.

I am indebted to my former professors and supervisors who contributed to my scientific and personal development: Professors José M. Vega Piqueres, Ernesto Carmona, David K. Apps, Ramón Serrano, and Manuel Losada.

Thanks a lot to De Gruyter and especially to my editors, Drs. Lena Stoll, Mareen Pagel, Ria Sengbusch (form. Fritz), Sabina Dabrowski, and Anna Bernhard, for their support during the writing of this book. Special thanks to Dr. Oleg Lebedev (former Senior Acquisitions Editor in Chemistry) for those first messages that triggered the whole process.

Many parts of this book were written in Alcaidesa, Southern Spain, many thanks to Mrs. Margarita Wrann-Hartmann, Ms. Patricia Espinosa Blaña, and Professor Robert W. McColl for making it possible. I also want to mention my hometown, Isla Cristina, whose sandy beaches on the Atlantic Coast of Andalucía are always an inspiration to me.

Finally, I thank my parents for their continued support throughout my life and also to my “German family” (Delia, Sean, and Chris).

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# 1 Food, nutrition, and diet

## 1.1 Basic concepts

### 1.1.1 Feeding, nutrition, food, and nutrients

Living organisms are open systems in thermodynamics terms, that is, they need to interchange matter and energy with the surrounding environment. In heterotrophic organisms like humans, this task is accomplished by taking up certain molecules from the exterior, using them as substrates for energy-releasing chemical reactions, utilizing this energy to perform the so-called biological functions, and finally, releasing the final products of those reactions into the environment.

The molecules we obtain from outside of our bodies are termed **nutrients** and they are usually the components of complex chemical systems known as **foods**. **Nutrition** is the process by which our bodies are able to obtain and assimilate the nutrients contained in a given food. Let us take milk as an example: this is the basic food for newborn mammals; however, milk is not a pure substance but it is composed of many different nutrients that are essential to survive during the first months of our lives. Nutrients include proteins, carbohydrates, lipids, minerals, and vitamins.

**Feeding (or eating)** is the process of finding food, introducing it into our mouths, masticating it (if necessary), and swallowing it; therefore, it is a voluntary, conscious, and educable action. Nutrition implies a myriad of chemobiological mechanisms integrated in the gastrointestinal tract and controlled in a non-voluntary fashion by the autonomic nervous system.

### 1.1.2 Diet and dietetics

**Diet** can be defined as the type and range of food that a person or an animal regularly eat [1]. With very few exceptions (like table sugar, composed almost exclusively of sucrose), the different types of food contain more than one nutrient; however, no food contain all the necessary nutrients in the required concentrations to sustain a healthy life. **Dietetics** is a branch of science that applies the current knowledge of physiology, biochemistry, epidemiology, and other subjects to the study of nutrition. The main objective of dietetics is the optimization of the human diet, which is not an easy task, as each individual may have his/her own particularities. Qualified dietitians perform a thorough study of their patients in order to prescribe an optimal diet for them considering genetic, metabolic, and even social and personal aspects.

### 1.1.3 Biological roles of nutrients

Nutrients play three major functions within our bodies:

- **Energetic**, by supplying the energy necessary to support all biological processes;
- **Structural**, by providing the basic units of the large molecules (biomolecules) that shape our bodies;
- **Regulatory**, by participating in the control of the chemical reactions that sustain life.

Nutrients can be classified into five basic types according to their chemical properties and/or biological roles: carbohydrates, lipids, proteins, vitamins, and minerals. A sixth nutrient with special properties has to be added to this list: water. Not all nutrients perform the same functions and some of them may play different ones (Table 1.1)

**Table 1.1:** Biological functions of nutrients.

Nutrient	Function		
	Energetic	Structural	Regulatory
Carbohydrates	+	+	+
Lipids	+	+	+
Proteins	+	+	+
Vitamins	–	–	+
Minerals	–	+	+
Water	–	+	+

Carbohydrates (Chapter 3) are generally regarded as energetic nutrients; however, they play a wide array of biological roles; thus, they are an important part of the extracellular matrix, they are involved in cellular recognition and can also attach to polypeptides, thereby regulating the biological activity of the resulting proteins. No wonder that the study of the important biological functions of the carbohydrates, glycobiology, is a very active field in natural sciences nowadays [2].

Lipids (Chapter 4) are regarded by many as the biomolecules with the highest content in energy per unit of mass, in fact, our bodies use some members of this family of compounds as an efficient storage and source of energy. However, lipids are a heterogeneous family of compounds that can play other biological roles; thus, phospholipids are essential to build the cellular membranes, whereas hormones like testosterone or progesterone are also lipids.

Proteins (Chapter 5) are rightly considered as “the molecules of life” with permission of the nucleic acids (whose role in nutrition is a matter of some debate, as

we shall see in Chapter 5). Proteins perform virtually every biological function, however, strictly speaking, the basic units that form proteins, **amino acids**, are the actual nutrients we need. There are only 20 proteinogenic amino acids, eight of them (nine during the childhood) are essential nutrients for humans.

Vitamins (Chapter 6) are a heterogeneous family of organic molecules with basic regulatory functions. They are also essential nutrients that can be classified according to their solubility in water. In many cases, the absence of a given vitamin in our diet may produce a specific disease or disorder (hypovitaminosis). Finally, due to the availability of dietary supplements, some disorders associated to an excess of some vitamins in the diet (hypervitaminosis) have also been reported.

Minerals (Chapter 7) are inorganic substances that usually appear on the earth surface as salts, although there are exceptions like selenium that has to be incorporated by humans as selenocystein or selenomethionine, two amino acids. We usually obtain minerals from other living organisms, although common salt and drinking water are also sources of minerals. These nutrients play a wide variety of functions like bone formation (calcium and phosphate), oxygen transport in the blood (iron), or modulation of enzymatic activities (calcium, magnesium, zinc, etc.). Minerals are also essential nutrients.

Water (Chapter 2) is a very special nutrient because although about 70% of human body weight is water we do not directly obtain energy from this molecule. Water participates directly or indirectly in the vast majority of biochemical reactions because its physicochemical properties are of paramount importance in the chemistry of life. Moreover, the three-dimensional structures of complex biological systems like cellular membranes and proteins are also determined by the interactions that biomolecules such as phospholipids, cholesterol (Chapter 4), and polypeptides (Chapter 5) have with water molecules.

## 1.2 Factors that influence diet

Dietary choices are influenced by a large number of interconnected factors. Although a profound analysis of these factors is beyond the scope of this book, a non-exhaustive list of some of them with brief comments of each is shown below:

- Availability of food. The major factor that influences an individual's diet is the range of foods available. For our ancestors, this basically depended on the geography and the climate, as primitive societies presumably collected the foods from their surroundings. The expansion of humans also implied expansion of food (crops and animals), that is, food globalization is not a modern trend but has been going on for tens of thousands of years [3]. During the last decades, this process has intensified and, along with the scientific and technological advances (see below), it has widened the range of available foods thereby changing dietary choices around the world. In developing countries, feeding a

growing human population is still a major issue of concern; however, the availability of food significantly increased worldwide during the second half of the twentieth century [4].

- Tradition, culture, and religion. This factor is related to the previous one because, as stated above, communities tend to eat what they have at hand. One example is the so-called Mediterranean diet, based on olive oil, grains, vegetables, and fish, that is, the foods available in the Middle East for millennia [5]. This diet is also deeply related to religious tradition [5] and has been subjected to important changes due to the contributions introduced along the history by the different Empires that have dwelt on the Mediterranean shores (Romans, Arabs, Spanish, Ottomans, among others) [6]. Religions have also played an important role by forbidding some foods like pork for Jews and Muslims.
- Technological advances. Humans are among the most successful species on the Biosphere: we have been able to adapt to virtually all sorts of ecosystems. One of the main reasons for this success is the development of technologies like agriculture, livestock farming, fishing, or cooking that has allowed us to obtain nutrients from many different sources. Advances in transportation have also been a major issue along the history, as illustrated by the changes in European diet that occurred after the discoveries by the Portuguese and Spaniards since the beginning of the fifteenth century [7]
- Socio-economic status. Regardless of the availability of food, it is also clear that the socio-economic status is a major determinant of dietary choice. This has been thoroughly studied in developed countries and, although the social mechanisms by which this actually happens are complex, people of lower socio-economic status tend to have energy-dense diets that have been associated with higher disease risk and mortality rates [8]
- Advertising. In the European Union, food and drink industry is the main manufacturing industry with a turnover of 1,098 billion euros in 2015, employing more than four million workers [9]. This means that food industry is a major actor in worldwide economy and also that competition is fierce not only within Europe but also between European and those from countries like USA and China and emerging economies like Brazil, India, or South Africa. As a consequence, food companies try to influence consumer behavior in order to increase their profits. To this end they spend millions of euros in advertising and lobbying, a topic that has been studied in detail elsewhere [10]
- Social and cultural factors. The perception of the ideal human body has evolved along our history [11]; however, during the second half of the twentieth century, the new trend of the “thin-ideal” has been imposed for females, whereas a muscular body is expected for males in order to be “attractive,” overweight being associated with negative features [12]. These trends, profusely broadcast by mass media, may be in conflict with the instincts and biological mechanisms developed during our history, when food shortage was probably

the norm [11]. In current developed societies, where food is widely accessible, many people, influenced by trends, think of themselves as being overweight and attempt to lose weight on some form of diet not usually prescribed by qualified professionals. In Europe and USA, the diet-industry is estimated to have an annual turnover in excess of \$150 billion. The problems associated with dieting are very complex and there are strong evidences suggesting that dieting may be promoting exactly the opposite of what it is intended to achieve [13].

### 1.3 Nutritional requirements and basic recommendations

Since the discovery that some diseases are linked to a lack or shortage of certain nutrients, like scurvy and vitamin C (Chapter 3), there has been an interest by scientists and authorities to propose guidelines for healthy diets [14]. During the last decades, an enormous quantity of information has been supplied by scientists and nowadays there are hundreds of scientific journals that regularly publish a myriad of articles about different aspects of food and nutrition. As a consequence, many public and private institutions are dedicated to evaluate and update this information and provide technical advice to health authorities worldwide. In the European Union, the European Food Safety Agency (EFSA) provides scientific advice and communication on many issues associated with food and nutrition. It was funded in 2002 following a series of food crises in the late 1990s. The EFSA operates independently of the European legislative and executive institutions (Commission, Council, Parliament), as well as Member States, and produces scientific opinions and advice that form the basis for European policies and legislation [15]. The remit of EFSA covers:

- Food and feed safety
- Nutrition
- Animal health and welfare
- Plant protection
- Plant health
- Impact of the food chain on the biodiversity of plant and animal habitats.

The available information about foods and nutrition is usually too technical for the standard consumer and, sometimes, even for health professionals. To solve this problem, health authorities publish the so-called “food-based dietary guidelines,” aimed at helping both professionals and the public to have a healthy lifestyle. According to the Food and Agriculture Organization of the United Nations (FAO),

food-based dietary guidelines (also known as dietary guidelines) are intended to establish a basis for public food and nutrition, health and agricultural policies and nutrition education programmes to foster healthy eating habits and lifestyles. They provide advice on foods, food groups and dietary patterns to provide the required nutrients to the general public to promote overall health and prevent chronic diseases [16].

Dietary guidelines elaborated by the authorities of many countries are available in the FAO web page (<http://www.fao.org/nutrition/education/food-dietary-guidelines/en/>). A significant example is the *Dietary Guidelines for Americans*, jointly published every five years by the US Department of Agriculture and Department of Health and Human Services. A summary that includes five major guidelines for the general public can be found at the beginning of this document. These guidelines, along with a few key recommendations, are the bases of a healthy diet not only for Americans but also for people worldwide [17]:

The Guidelines:

1. Follow a healthy eating pattern across the lifespan. All food and beverage choices matter. Choose a healthy eating pattern at an appropriate calorie level to help achieve and maintain a healthy body weight, support nutrient adequacy, and reduce the risk of chronic disease.
2. Focus on variety, nutrient density, and amount. To meet nutrient needs within calorie limits, choose a variety of nutrient-dense foods across and within all food groups in recommended amounts.
3. Limit calories from added sugars and saturated fats and reduce sodium intake. Consume an eating pattern low in added sugars, saturated fats, and sodium. Cut back on foods and beverages higher in these components to amounts that fit within healthy eating patterns.
4. Shift to healthier food and beverage choices. Choose nutrient-dense foods and beverages across and within all food groups in place of less healthy choices. Consider cultural and personal preferences to make these shifts easier to accomplish and maintain.
5. Support healthy eating patterns for all. Everyone has a role in helping to create and support healthy eating patterns in multiple settings nationwide, from home to school to work to communities.

Several “Key Recommendations” provide further guidance on how individuals can follow these five guidelines [17]:

Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.

A healthy eating pattern includes:

- A variety of vegetables from all of the subgroups – dark green, red and orange, legumes (beans and peas), starchy, and other
- Fruits, especially whole fruits
- Grains, at least half of which are whole grains
- Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages

- A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products
- Oils

A healthy eating pattern limits:

- Saturated fats and trans fats, added sugars, and sodium
- Consume less than 10 percent of calories per day from added sugars
- Consume less than 10 percent of calories per day from saturated fats
- Consume less than 2,300 milligrams (mg) per day of sodium
- If alcohol is consumed, it should be consumed in moderation – up to one drink per day for women and up to two drinks per day for men – and only by adults of legal drinking age.

In tandem with the recommendations above, Americans of all ages – children, adolescents, adults, and older adults – should meet the Physical Activity Guidelines for Americans<sup>1</sup> to help promote health and reduce the risk of chronic disease.

In an effort to make dietary guidelines and recommendations easily available to the general public, many health authorities publish visual representations such as pyramids and plates that inform on the recommended relative contributions of different food groups to the diet [17, 19]. Some examples are shown in Figure 1.1.

## 1.4 Sustainability

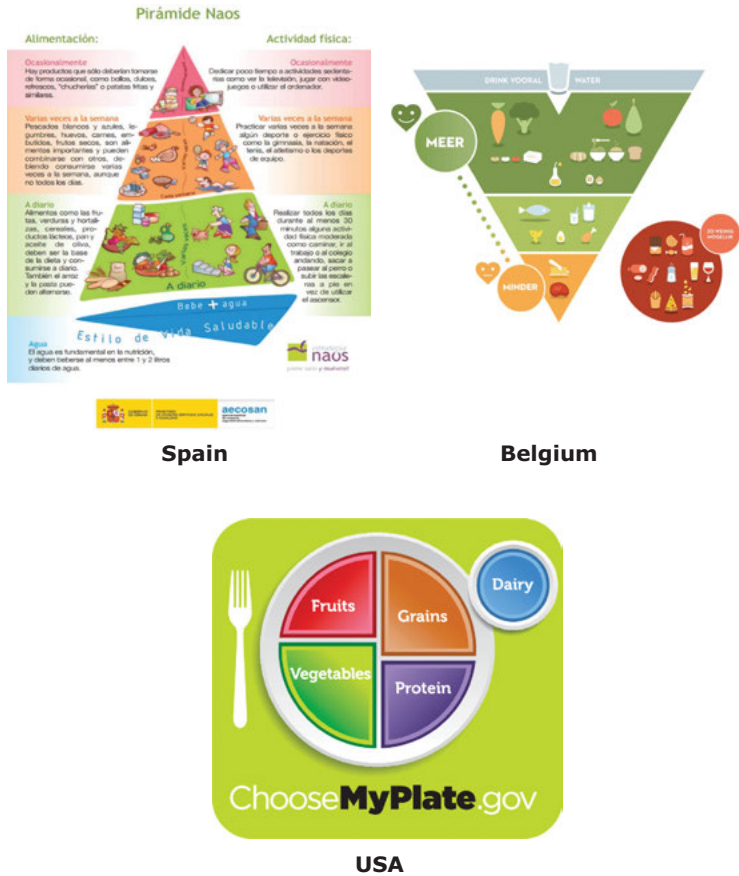
Food production exerts a considerable impact of the planet's resources, while many people are not adequately nourished. Data on the environmental impact on current food (especially crop and livestock) production and consumption are overwhelming [19]:

- It contributes to 20–30% of anthropogenic greenhouse gas emissions.
- It is the leading cause of deforestation, land use change, and biodiversity loss.
- It accounts for 70% of all human water use, being a major source of water pollution.
- Unsustainable fishing practices deplete stocks of species we consume and also cause wider disruption to the marine environment.

The impacts of climatic and environmental change are already making food production more difficult and unpredictable in many regions of the world. In order to address the multiple social, health, and environmental challenges caused by food systems, it is necessary to move toward diets that are both healthy and respectful of

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<sup>1</sup> Available in [18]



**Figure 1.1:** Visual representations of official food-based dietary guidelines from different countries.

environmental limits. In 2016, 83 countries out of a possible total of 215 had official food-based dietary guidelines of any kind; however, only four countries had included sustainability in their guidelines: Brazil, Sweden, Qatar, and Germany. Dietary patterns that have low environmental impacts can also be consistent with good health; therefore, a global effort must be made in order to implement sustainable systems of food production as well as healthy dietary patterns. Sustainability-oriented dietary guidelines can be invaluable tools to accomplish these tasks [19].

### 1.5 Personalized dietary patterns

Nowadays there is a general consensus about the association of overweight and obesity with conditions and diseases like type II diabetes, cardiovascular diseases, and

certain types of cancer (Chapter 14). Although obesity is considered a complex pathology that results from the interaction of environmental and genetic factors, dietary habits play a significant role in the increasing incidence of this disease; however, interventions aimed at altering these habits in order to improve public health have had limited impact so far. Some authors argue that personalization of interventions may be more effective in changing eating behaviors than general guidelines and recommendations. Personalized nutrition uses information on individual characteristics to develop targeted nutritional advice that assists people to achieve a dietary change that can result in health benefits. The concept of “precision nutrition” further suggests that this kind of interventions can be achieved by understanding the complex relationships among an individual, his/her food consumption, and his/her phenotype (including health) [20]. Some relatively new scientific disciplines are involved in the development of personalized/precision nutrition. These include:

- Nutrigenetics, the study of the effects of genetic variation on dietary response [21].
- Nutrigenomics, the study on the evolutionary aspects of diet and the role of nutrients in gene expression [21].
- Exposome science, concerned with the collection of environmental factors (stress, physical activity and diet) to which an individual is exposed and which may affect health [20].

These disciplines are based on a series of high-throughput technologies, generically known as “omics,” that allows the identification, characterization, and quantification of all biomolecules that are involved in the structure, function, and/or dynamics of a given biological system [22]. In the case of nutrition, the main “omics” involved are:

- Epigenomics, studies the whole set of epigenetic changes that modify the expression and function of the genetic material of an organism (Chapter 14).
- Metabolomics, the large-scale study of small molecules, commonly known as metabolites, within cells, tissues, or organisms. Collectively, these small molecules (within a mass range of 50–1,500 daltons) and their interactions within a biological system are known as the “metabolome” [23].
- Microbiomics, the study of the microbiome, the totality of microbes in specific environments, such as the human gut [20].

According to Ordovas and colleagues [20], there are two key questions with respect to personalized nutrition:

- Can this approach produce greater, more appropriate, and sustained changes in behavior than conventional approaches?
- Do these changes result in better health and well-being?

Some limited information suggests that the answer to the first of these questions is yes, but the second question remains unanswered, because no study has been carried out at a large scale, in an appropriate population group and over a sufficiently long time. These authors reached the conclusion that “much research and regulation is required before personalized nutrition can deliver the expected benefits” [20].

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## 2 Water

### 2.1 Introduction

In the summer of the year 2018, subglacial liquid water was reported in Mars [1]. This finding prompted a worldwide expectation about the possibility of the existence of life in our neighboring planet because, instinctively and rightly, we humans link water in its liquid form to life.

Water is a stable molecule from the chemical point of view under the conditions prevailing on Earth, thus its occurrence not only in the atmosphere and the crust but also in the mantle [2]. Liquid water presents a large number of physico-chemical properties that make it essential for what we call “life”: it acts as a building material, solvent, reaction medium, reactant, carrier for nutrients and waste products, thermo-regulator, lubricant, and shock absorber [3]. Consequently, the chemical reactions of living organisms are directly or indirectly determined by water even when it is not explicitly mentioned.

One of the most important roles of water in the Biosphere is as an electron donor in oxygenic photosynthesis, a biochemical process devised by the ancestors of cyanobacteria. When these organisms developed the capacity to use water to capture the energy from the sun and transform it into biologically useful chemical energy, they changed our planet’s history from that point on. In oxygenic photosynthesis, water molecules are split using the energy from sunlight and molecular oxygen ( $O_2$ ) is released as a by-product. This was a spectacular breakthrough in Earth’s history that led to the so-called “Great Oxidation Event” (GOE), which very likely implied the annihilation of many organisms; however, the availability of oxygen triggered the evolution of aerobic respiration and novel biosynthetic pathways, facilitating complex multicellularity and the biodiversity we observe today [4]. Oxygenic photosynthesis (and, thus, water) is considered the largest source of  $O_2$  in the atmosphere [5].

Another point worth of consideration is that although water is known as “the universal solvent,” it does not dissolve many molecules. Liquid water has a very stable dynamic three-dimensional structure in which the hydrogen bond plays an essential role. Some molecules (hydrophilic or “water-loving”) integrate into this structure establishing an energetically stable system, whereas others (hydrophobic or “water-hating”) disrupt the water structure and, consequently, they are “rejected,” that is, not dissolved. The most important consequence for life of this property of liquid water is that many biomolecules adapt their structures to the constraints imposed by the surrounding water molecules in order to fit within them, thereby yielding stable biomolecular complexes. This is how water, a “simple” chemical substance, fundamentally determines the structure (and thus the function) of proteins, biological membranes, or chromatin, composed by thousands of atoms [6].

## 2.2 Water as a nutrient

Water is the most abundant chemical component of the body, comprising 50–60% of an adult body weight with a range from 45% to 75% according to some sources and from 30% to 70% according to others [7, 8]. Among the factors that can alter the ratio of total body water to weight are sex, age, level of fatness/leanness, climate, salt intake, and certain diseases [7]. Fatness is one of the major factors that determine the proportion of water in the body, actually, the percentage of water content with respect to the fat-free mass is less variable than with respect to total body weight, this value being around 73% [9]. Water is not evenly distributed within our body: in adults, about two-thirds of total water is in the intracellular space, whereas one-third is extracellular [3]. The volume and composition of the intracellular and extracellular fluids (ICF and ECF) must be maintained within certain limits compatible with life and this is accomplished by a set of complex homeostatic physiological and biochemical processes.

Water is a very special nutrient: although it is very abundant in our body it is often ignored in reports of dietary surveys and nutrition, the attention being more focused on the minerals and other substances dissolved in it. However, we need water and cannot synthesize it by ourselves (at least, in the quantities we need); therefore, it is an essential nutrient; then, why has it been regarded as “neglected, unappreciated and under researched” [8]? Probably, this is due to a number of peculiarities of this molecule, among of which are: (1) the way our metabolism utilizes water differs from other nutrients; (2) it is an “inorganic” molecule, composed by one atom of oxygen and two of hydrogen, that is, it does not contain carbon (C), the element considered to be characteristic of life; and (3) it does not require digestion to be incorporated into our bodies.

## 2.3 Water balance in the body: inputs, outputs, and regulation

Intake and loss of water must be more or less equal over a 24-h period. Water intakes are normally composed of beverages, food, and metabolically produced water (see below); conversely, water is continually lost from the body through respiration, urine formation, insensible loss (evaporation from lungs and skin), sweat, and feces. Direct measurements of total amount of water gained and lost are not possible, which means that significant variations of inputs and outputs of water are observed in different studies, as illustrated in Table 2.1, that show data taken from two different sources [3, 10]. The assessment of water balance is further complicated by the fact that these data can be subjected to important changes due to factors such as physical activity, climate, and individual physiology [8].

At the molecular level, water is transported across biological membranes by three different mechanisms: (1) by diffusion through the lipid matrix; (2) through some

**Table 2.1:** Water balance in sedentary adults living in temperate climate.

Water inputs (milliliters/day)			Water outputs (milliliters/day)		
Beverages	1,575 <sup>a</sup>	>1,000 <sup>b</sup>	Respiration & sweat	750 <sup>a</sup>	900 <sup>b</sup>
Foods	675 <sup>a</sup>	1,000 <sup>b</sup>	Feces	100 <sup>a</sup>	200 <sup>b</sup>
Metabolic water	300 <sup>a</sup>	400 <sup>b</sup>	Urine	1,600 <sup>a</sup>	600–2,400 <sup>b</sup>
Total	2,550 <sup>a</sup>	2,400 <sup>b</sup>	Total	2,550 <sup>a</sup>	1,700–3,500

Data taken from references [3]<sup>a</sup> and [10]<sup>b</sup>.

membrane-embedded channels or solute transporters; and (3) through specific water channels known as aquaporins. A common feature to these mechanisms is that water movement is driven by gradients of its own chemical potential [11, 12]. The chemical potential of water in our bodies is essentially determined by the concentration of solutes or electrolytes in the biological fluids, usually measured as the number of moles of osmotically active species (osmoles) per kilogram of water (“osmolality”) or per liter of solution (“osmolarity”). Osmolarity and osmolality values do not differ much in dilute solutions, therefore, they are often used interchangeably [3]. The most important contributors to osmolarity in the body fluids are electrolytes like sodium ( $\text{Na}^+$ ), chloride ( $\text{Cl}^-$ ), potassium ( $\text{K}^+$ ), calcium ( $\text{Ca}^{2+}$ ), magnesium ( $\text{Mg}^{2+}$ ), sulfate ( $\text{SO}_4^{2-}$ ), or phosphate ( $\text{PO}_4^{3-}$ ) and solutes such as glucose or urea [13, 14].

Total body water is precisely maintained under moderate conditions (within 0.2% of total weight over a 24-h period) by a complex system involving the hypothalamus, the neurohypophysis, and the kidneys. Essentially, it is a feedback mechanism in which some membrane proteins (osmoreceptors) located on the hypothalamus sense increases in plasma osmolality thus triggering secretion of vasopressin (also known as antidiuretic hormone or ADH) to the bloodstream and thirst. Vasopressin increases reabsorption of water in the kidneys, a process that, along with drinking, should restore osmolarity to normal levels [3, 15]. By means of this physiological process, osmolarity of plasma is tightly controlled and rarely varies by more than 2% around a set point of 0.280–0.290 “osmoles/L”, which increases somewhat with age [16]. In clinical studies, plasma osmolality can be directly measured (by the degree of freezing point depression, for example) or predicted by using equations that consider plasma concentrations of sodium, potassium, glucose, and urea [13].

Not only maintaining the overall water balance in the body is essential for survival but its distribution between the different compartments within living organisms must also be carefully regulated, as water determines the absorption and distribution of all nutrients [10]. Cells spend a significant amount of energy in active transport of solutes and electrolytes across their membranes in order to maintain an appropriate composition inside and outside, thereby adjusting the distribution of water and, consequently, their own volume [15, 17] (see Chapter 13 for more details on transport of water and electrolytes).

## 2.4 Water requirements

Human water requirements depend on a number of factors such as age, metabolism, climate, physical activity, or diet; however, due to the precise mechanisms of water balance control, normal hydration is compatible with a wide range of fluid intake in healthy adults. Inputs are composed of three major sources: drinking water and beverages (70–80% of total intake), food (20–30%), and some water produced from the oxidation of macronutrients (less than 2%). This relationship is not fixed and depends on the type of beverages and food we ingest, which may contain variable contents of water: from 85 to >90% in the former and from 40 to >80% in the latter [3].

Normal hydration status is “the presumed condition of healthy individuals who maintain water balance,” according to the study of the European Food Safety Authority published in 2010 about dietary reference values for total water intakes [16]. In this report, a number of values for adequate intakes (AIs) of water were recommended:

- 100–190 milliliters (ml)/kg per day during the first half of the first year of life (based on water intake from human milk in exclusively breast-fed infants);
- 800–1,000 ml/day for the age period 6–12 months;
- 1,100–1,200 ml/day during the second year of life (value is defined by interpolation, as intake data are not available);
- 1,300 ml/day for boys and girls 2–3 years of age;
- 1,600 ml/day for boys and girls 4–8 years of age;
- 2,100 ml/day for boys 9–13 years of age; 1,900 ml/day for girls 9–13 years of age;
- Adolescents of 14 years and older are considered as adults with respect to adequate water intake and the adult values apply;
- Adults: females would have to be 2.0 liters (l)/day and for males 2.5 l/day. Same AIs are recommended for the elderly as for adults, because both renal concentrating capacity and thirst are decreasing with age;
- No data on habitual water intake in pregnant women were found and the same water intake as in non-pregnant women plus an increase in proportion to the increase in energy intake (300 ml/day) was proposed;
- For lactating women, 700 ml/day above the AIs of non-lactating women of the same age.

The EFSA Panel also included several important considerations concerning these values:

- Recommended AIs apply only under conditions of moderate environmental temperature and physical activity levels.
- Water losses incurred under extreme conditions of external temperature and physical exercise, which can be up to about 8,000 ml/day, have to be replaced with appropriate amounts. In such instances, concomitant losses of electrolytes have to be replaced adequately to avoid hypo-osmolar disturbances.

- Too high intakes of water which cannot be compensated by the excretion of very dilute urine (maximum urine volumes of about one liter/hour in adults) can lead to hyponatremic, hypo-osmolar water intoxication with cerebral edema.
- Maximum daily amount of water that can be tolerated have not been defined.
- The reference values for total water intake include water from drinking water, beverages of all kind, and from food moisture.

The EFSA Report has certain limitations due to the uncertainties in the methods used to assess water intake from food and beverages in different European countries. This means that a consistent and validated methodology to reduce potential sources of errors in the elaboration of these reports is very much needed [18].

The process of losing body water that may eventually lead to a deficit is called dehydration, which can be classified as isotonic, hypertonic, or hypotonic:

- Isotonic dehydration occurs when both water and solutes are lost from the ECF, e.g. through vomiting, diarrhea, or inadequate intake.
- Hypertonic dehydration occurs when water loss exceeds salt loss, e.g. through inadequate water intake, excessive sweating, osmotic diuresis, or diuretic drugs.
- Hypotonic dehydration occurs when more sodium than water is lost, e.g. in some instances of high sweat or gastrointestinal fluid losses or when fluid and electrolyte deficits are treated with water replacement only.

Increasing dehydration has been linked to reductions in exercise performance, thermoregulation, and appetite (fluid losses of more than 1%); severe performance decrements, difficulties in concentration, headaches, irritability, and sleepiness as well as increase in body temperature and in respiratory rates (fluid deficits of 4%), and, ultimately, death (fluid deficits of 8%). Dehydration has also been linked to impairment of cognitive performance and motor function, such as fatigue, mood, target shooting, discrimination, choice reaction time, visual-motor tracking, short-term and long-term memory, and attention. Populations at particular risk of dehydration include the very young and the elderly; therefore, assessment of the hydration status is of paramount importance for health. Among the techniques that can be used to accomplish this goal are: measurement of body weight, tracer techniques, bioelectrical impedance, determination of plasma osmolarity, and measures of some urine indices [3, 16].

## 2.5 Water resources and supply

Water is not only necessary for direct human consumption but also for food production including agriculture, livestock breeding, and processing, activities that require water of varying quality. The Guidelines for drinking-water quality published by the World Health Organization [19] states that “water is essential to sustain life, and a

satisfactory (adequate, safe and accessible) supply must be available to all [...]. Safe drinking-water [...] does not represent any significant risk to health over a lifetime of consumption, including different sensitivities that may occur between life stages.”

Water supply is one of the major challenges for humankind because the number of people who do not have access to water without any potential health hazards is estimated to be around 3.5–4 billion, nearly five times the current United Nations estimate [20]. This will continue to be a major problem in the near future, as the world’s population is projected to increase by slightly more than one billion people over the next 13 years, reaching 8.6 billion in 2030, and to increase further to 9.8 billion in 2050 and 11.2 billion by 2100 according to the United Nations [21]. Actually the so-called “water crisis” is listed among the most important risks by the World Economic Forum in its last report issued on 2018 [22].

One of the most important bottlenecks for safe water supply is the shortage of freshwater sources in our planet. Although more than 70% of Earth’s surface is covered by water, about 97% is saline and is not easily usable for human use and consumption, only around 2.5% is fresh water. A mere 1.2% of the latter is on the surface, the rest being held in glaciers and ice caps (65.7%), as well as in groundwater (30%). To complicate matters, only a low percentage of surface water is in lakes (21%) or rivers (0.5%), the rest being as permafrost (69%) (Table 2.2) [23]. Moreover, global distribution is not the complete picture because freshwater sources are unevenly distributed and sometimes they are not close to populated or agricultural

**Table 2.2:** Global use of rainwater.

Total rainwater 110.000 km <sup>3</sup> /year			
Blue water (groundwater, rivers and lakes)		Green water (available for uptake by plants)	
<b>Total</b>	40,000 km <sup>3</sup>	<b>Total</b>	70,000 km <sup>3</sup>
<b>Withdrawn for human usage</b>	4,000 km <sup>3</sup>		
<b>Agriculture</b> (irrigation, livestock breeding and washing, aquaculture)	2,760 km <sup>3</sup> (*)	<b>Agriculture</b> (rain-fed crops)	6,400 km <sup>3</sup>
<b>Industry</b> (including food and beverages industry)	760 km <sup>3</sup> (*)	<b>Evaporated</b> (from forests, uncultivated vegetation, and wetlands)	Rest
<b>Domestic</b> (including water for drinking and cooking)	480 km <sup>3</sup> (*)		

Elaborated with data taken from references [23, 28–30].

(\*) Average global values. A significant variability occurs worldwide. See AQUASTAT website for further details.

areas; therefore, sustainable water technologies must be developed and made available worldwide to ensure a proper supply for most people [24, 25].

In socio-economic and environmental terms, water resources can be classified as renewable and non-renewable. Groundwater and surface water are considered renewable whereas deep aquifers, which do not have a significant replenishment rate on the human time scale, are non-renewable water resources [26]. Unfortunately, not all surface water or groundwater is accessible for use, actually, exploitable water resources are significantly smaller than the natural resources and depend on factors such as the capability of storing floodwater behind dams or extracting groundwater, among others [27].

## 2.6 The importance of water in food production

Water is not only an essential nutrient for all living organisms but it is also crucial in many aspects of food production and processing: irrigation, livestock watering, aquaculture (initial production) or as an ingredient, transport medium, and hygiene aid (processing). Both water and food may be vehicles for the transmission of infectious agents or toxic chemicals and people can be exposed to these agents in three different ways:

- Through contaminated water incorporated into foods
- Through foods irrigated with or harvested from contaminated water
- Through foods that have come into contact with contaminated water during processing

Therefore, a proper supply of quality water is vital to food security and production [31]. In the European Union, the quality of the water used in food manufacturing must meet the basic standards governing the quality of drinking water [32] amended in 2003, 2009, and 2015 proposed for a revised drinking water directive on 1 February 2018: this initiative is scheduled to be discussed by the European Parliament during the term starting on 2 July 2019.

Atmospheric precipitation on the continents and islands is the origin of the renewable water resources. It has been estimated that an average of 110,000 km<sup>3</sup> of rain falls over the continents annually. More than 70,000 km<sup>3</sup> infiltrates the soil and is available for uptake by plants, this fraction is known as “green water.” Around 40,000 km<sup>3</sup> (“blue water”) flows in groundwater and surface water (river, lakes). Green water can be either productive, if taken up by crops or natural vegetation, or non-productive, if evaporated from soil and open water, actually, only 6,400 km<sup>3</sup> of rainwater is estimated to fall on cultivated areas, the rest being evaporated from forest, natural (uncultivated) vegetation, and wetlands. As far as blue water is concerned, only 10% of it is withdrawn for human use (around 4,000 km<sup>3</sup>): agriculture uses an average 69%, including irrigation, livestock breeding, and washing and aquaculture; 20% is for

industrial uses, which includes the food and beverage industry, and the rest (around 12%) is for domestic use, including drinking and cooking water (Table 2.2).

Rain-fed agriculture, that depends on “green water,” covers 80% of the world’s cultivated land, and is responsible for about 60% of crop production, whereas irrigated agriculture (that uses “blue water” although sometimes relies on green water in addition [26]) covers about 20% of cultivated land and accounts for 40% of global food production.

The food processing and manufacturing industry uses water for a number of processes such as transport, steam generation, cooling, and cleaning and also as an ingredient [33]. This means an additional 5–10% of freshwater consumption with respect to freshwater withdrawal for irrigation in a country like USA or 30% of all the water used for manufacturing in Australia [34]. In the European Union, the food and beverage industry is the largest manufacturing sector in terms of turnover, value-added, and employment and it has been reported to be responsible for 1.8% of Europe’s total water use [35]. However, water supply is not the only problem, it is also very important to understand how demand, sources of pollution, water reuse, and contamination of food through water affect food safety. Pressures on water demand are expected to increase in the next decades creating a vicious cycle: increasing exploitation of water resources leads to more water pollution that further reduces the availability of clean water. Sustainable alternatives need to be implemented in all areas of human activity, but especially during food production and processing [25, 31].

Another point of interest is the possibility to recycle water for subsequent uses. This is feasible in water for industrial and domestic uses, where most of the water returns to rivers after use; however, in agriculture, a large part of water is released in the atmosphere by evapotranspiration because this is the physiological mechanism by which plants take up nutrients from the soil [28].

Two very important concepts, “water footprint” and “virtual water,” have been introduced to correctly assess the problems facing water supply in the next future:

- The water footprint is “a measure of human’s appropriation of freshwater resources [...] measured in terms of water volumes consumed (evaporated or incorporated into a product) or polluted per unit of time” [36]. The interesting feature of this concept is that it is calculated considering not only blue and green water consumption but also the wastewater production (“grey water”).
- The “virtual water” content of an agricultural or industrial product is the overall water used in the production process of that product. Virtual water allows the calculation of “hidden water” trade flows between countries, for example, a water-scarce country imports products that require a lot of water in their production and export products or services that require less water. This implies net import of virtual water.

The water footprint of a certain good is calculated considering its virtual water content [36, 37]. Table 2.3 shows the water footprint of a number of food products.

**Table 2.3:** Water footprint of some selected food products from vegetable and animal origin.

Product	Water footprint (m <sup>3</sup> /Ton or l/kg)
Sugar crops	197
Vegetables	322
Starchy roots	387
Fruits	962
Cereals	1,644
Oil crops	2,364
Legumes	4,055
Nuts	9,063
Milk	1,020
Eggs	3,265
Chicken meat	4,325
Butter	5,553
Pig meat	5,988
Sheep/goat meat	8,763
Beef	15,415

Source: [38].

## 2.7 The importance of water in the properties of foods

The water content of a food plays a major role in its properties; however, rather than the total moisture content, it is “water activity” ( $a_w$ ) the parameter that has been shown to correlate more closely with microbial, chemical, and physical properties of foods. Water activity is a thermodynamic concept, intrinsically linked to the concept of (water) chemical potential, and defined as the ratio of the fugacity of water ( $f_w$ ) in a system and the fugacity ( $f_w^0$ ) of pure liquid water at a given temperature. Fugacity is a measure of the escaping tendency of a particular component within a system and can be used to calculate the deviation from the ideality in a gas phase. It can be replaced by the total or partial vapor pressure in the equilibrium with an error less than 0.1% in many systems under normal conditions. Therefore, a working definition of  $a_w$  may be the ratio of the equilibrium partial vapor pressure of water in the system ( $p_w$ ) and the equilibrium partial vapor

pressure ( $p_w^o$ ) of pure liquid water at the same temperature and total pressure [39]. Although there may be inherent problems with applying the concept of  $a_w$ , which is an equilibrium thermodynamic concept, it may help to understand what happens in systems, such as foods, that are not usually in strict equilibrium [40].

Water activity is considered one of the most important parameters in food preservation and processing. William J. Scott was the first to show in 1953 that there was a significant correlation between  $a_w$  and microbial growth and toxin production in foods. Subsequent studies during the 1960s and 1970s shed information about this parameter and its influence on the chemical, enzymatic, and physical stability of foods that affected the characteristics (color, flavor, texture, etc.) and acceptability of raw and processed food products [41]. Consequently, several food preservation techniques rely on controlling (normally decreasing)  $a_w$  in order to reduce the rates of microbial growth and chemical reactions by using food stability maps as a function of water activity [40].

Water activity is related to the moisture content of a food in complex way: an increase in  $a_w$  is usually accompanied by an increase in water content in a non-linear fashion. The relationship between water activity and moisture content at a given temperature is called the moisture (or water) sorption isotherm, which illustrates the steady-state amount of water held by the food solids as a function of  $a_w$  (or percentage of relative humidity) at constant temperature. Water vapor sorption by foods depends on many factors, including chemical composition, physical-chemical state of ingredients, and physical structure. This makes sorption isotherms valuable tools for food scientists because they can be used to predict which reactions will decrease stability at a given moisture or which ingredient can be used to change the  $a_w$  in order to increase the stability. They also help to predict moisture gain or loss in a package with known moisture permeability [40].

Glass transition is also an important water-related concept in food technology that has been reported to play an important role in the properties of dehydrated and frozen foods. It is a relaxation process occurring in food solids that can be defined as a transformation of a supercooled liquid to a highly viscous, solid-like glass. Unlike water activity, a property of water molecules, glass transition is a property of amorphous food components (such as carbohydrates and proteins) which is affected by the extent of water plasticization (softening) of the solids [42].

Glass transition and water activity are two completely different parameters, but they are complementary and both can be used to explain food deterioration or stability. The  $a_w$  is an important parameter affecting microbial growth, whereas glass transition is a property related to changes in food structure and microstructure, crystallization, rates of diffusion-controlled reactions, and, possibly, stabilization of microbial cells and spores [42].

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## 3 Carbohydrates

### 3.1 Definition, terminology, and classification

Carbohydrates are a family of biomolecules composed, in principle, by carbon (C), hydrogen (H), and oxygen (O) atoms whose basic general formula is  $C_n(H_2O)_m$ . The fact that many carbohydrates have two atoms of hydrogen per atom of oxygen in their molecules is responsible for the somewhat misleading name that these molecules have, as “hydrate” means “containing water.” Carbohydrates have no water in their chemical composition, as we shall see in this Chapter, although they are usually hydrated to different degrees both *in vivo* and *in vitro*.

Carbohydrates are usually constituted by an indeterminate number of basic units linked forming polymers. The connections among these units may occur by means of different linkage types, thereby allowing many structural variations [1].

There are several important terms related to carbohydrates:

- **Monosaccharides:** They are the basic non-hydrolyzable units of carbohydrates. Monosaccharides can be chemically altered yielding derivatives that may also form polymers. These alterations may involve the addition of elements such as nitrogen (N), sulfur (S), or phosphorus (P).
- **Oligosaccharides.** Molecules composed of 2 to 12 (20 for some authors) linked units (residues) of monosaccharides by a specific type of chemical bond known as **glycosidic bond**. Oligosaccharides are denoted according to the number of monosaccharide residues they have: **disaccharides** (2 units), **trisaccharides** (3), **tetrasaccharides** (4), and so on.
- **Sugar:** Many monosaccharides and disaccharides are sweet, hence their trivial name **sugars**, although table sugar is only composed of sucrose, a disaccharide. Carbohydrates are also known as **glycids** (from the Greek *glykys*, *glykeros*: sweet) or **saccharides** (from the latin *saccharum*: sugar).
- **Polysaccharides:** Polymers composed of more than 12 (or 20) residues of monosaccharides. Polysaccharides are named as **homo-** or **heteropolysaccharides** depending on whether they are composed of a single type or more than one type of monosaccharide, respectively. Oligo- and polysaccharides can be linear or branched and they may undergo further chemical modifications (see below).
- **Glycan:** Although this term is considered a synonym of polysaccharide by the IUPAC [2], biochemists use it for those oligo- or polysaccharides that bind to other biomolecules.
- **Glycoconjugates:** Biochemical compounds consisting of a glycan moiety linked to proteins or lipids. The process by which a glycan is attached to another biomolecule is known as glycosylation when it is catalyzed by an enzyme, or

glycation when it is just a chemical non-mediated process. There are several types of glycoconjugates:

- **Glycoproteins/glycopeptides:** Proteins/peptides (Chapter 5) containing oligosaccharide chains covalently attached to amino acid side chains.
- **Peptidoglycans:** Generally composed of linear heteropolysaccharides covalently linked with short peptides.
- **Glycolipids:** Lipids (usually 1,2-diacylglycerols, see Chapter 4) with a monosaccharide or oligosaccharide linked.
- **Lipopolysaccharides:** Complex glycolipids that occur in the outer membrane of Gram-negative bacteria. They induce immune response in many species, including humans.

The large number of different basic units (monosaccharides and derivatives) that can be linked by several types of chemical bonds, along with the possibility to form glycoconjugates allow carbohydrates to constitute or participate in an ample variety of biological compounds. Some members of this family, such as the extracellular polysaccharides of plants, fungi, and arthropods (cellulose and chitin), are the most abundant biomolecules on Earth. Glycoconjugates are also very common: more than 50% of all human proteins are estimated to be glycosylated. Therefore, carbohydrates are of paramount importance for life, both qualitatively and quantitatively, and they are involved in a wide array of biological functions [3]:

- Energy supply
- Formation of biological structures
- Morphogenesis
- Protein folding
- Transcriptional regulation
- Information exchange between cells
- Cellular recognition

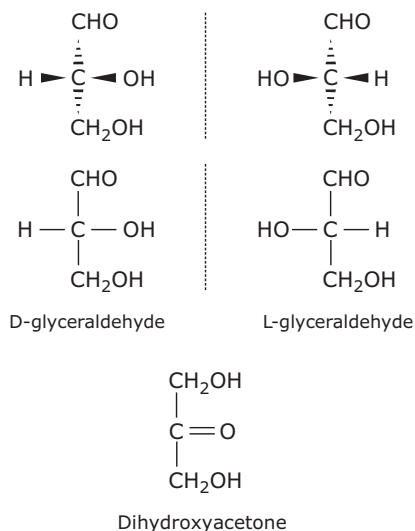
The structural and functional diversity of carbohydrates has led to the development of a relatively new branch of Biochemistry and Molecular Biology, Glycobiology, which can be defined as “the study of the structure, biosynthesis, biology and evolution of saccharides [. . .] that are widely distributed in nature and of the proteins that recognize them” [4]. Glycobiology aims at integrating traditional carbohydrate chemistry and biochemistry with the current knowledge of molecular and cellular biology. Other interesting terms are glycomics, the study of the glycome, that is, all the glycans that a cell or tissue produces under specified conditions, and glycoproteomics, whose goal is the identification and quantitation of the glycans that interact with proteins. The last two terms describe those aspects of glycobiology that require a systems-level analysis to be appropriately studied [5].

This Chapter will focus mainly on the importance of the energetic function of carbohydrates and the composition and biological roles of the members of this family most commonly involved in human nutrition.

## 3.2 Monosaccharides and oligosaccharides

### 3.2.1 Monosaccharides

Monosaccharides are the only members of the carbohydrates that respond to the molecular formula  $(\text{CH}_2\text{O})_n$ , that is, in the general formula shown at the beginning of this chapter  $[\text{C}_n(\text{H}_2\text{O})_m]$ , they are the particular case in which “n” is equal to “m.” Chemically, monosaccharides are polyhydroxy aldehydes (**aldoses**) or polyhydroxy ketones (**ketoses**), typically consisting of a chain of hydroxymethylene ( $-\text{CHOH}$ ) units (with the only exception of dihydroxyacetone), which terminates at one end with a hydroxymethyl group ( $-\text{CH}_2\text{OH}$ ) and at the other with an aldehyde group ( $-\text{CHO}$ , aldoses) or an  $\alpha$ -hydroxy ketone group ( $\text{HOCH}_2\text{-CO-}$ , ketoses) [6]. Their chemical formulae are often depicted in the two-dimensional Fischer projection (Figures 3.1 to 3.3), in which the carbon atoms are aligned vertically and numbered from top to bottom following the rules of Organic Chemistry nomenclature (the carbon of the carbonyl group is C-1 in aldoses and C-2 in ketoses). This projection was originally proposed by Emil Fischer in the late nineteenth century for



**Figure 3.1:** Chemical structures of glyceraldehyde and dihydroxyacetone.

monosaccharides and, although problematic for many organic molecules, it remains acceptable nowadays for carbohydrates and their derivatives [7].

Glyceraldehyde is the simplest aldose and dihydroxyacetone is the simplest ketose (Figure 3.1). Addition of successive hydroxymethylene units to these molecules after the carbonyl group can be used to formulate the aldoses and ketoses families, respectively (Figure 3.2). From the biological point of view, the most prominent monosaccharides are those containing between three and seven carbon atoms, but, in nutritional terms, the most important and abundant are those that have six  $[(\text{CH}_2\text{O})_6 \text{ or } \text{C}_6\text{H}_{12}\text{O}_6]$ , the so-called hexoses (Table 3.1). Hexoses containing an aldehyde group are known as aldohexoses and those containing an  $\alpha$ -hydroxy ketone group, ketohexoses or hexuloses.

With the only exception of dihydroxyacetone, all monosaccharides present a number of chiral carbons (linked to four different atoms or atom groups) equal to that of hydromethylene units: aldoses of  $n$  carbon atoms contain  $n-2$  chiral centers, whereas ketoses contain  $n-3$ . Molecules that differ only in the configuration of one or more chiral carbons are known as **stereoisomers**. The number of possible stereoisomers for aldoses and ketoses are  $2^{n-2}$  and  $2^{n-3}$ , respectively [6], for example, aldohexoses have four stereogenic centers (6-2), that is, 16 possible isomeric forms, whereas ketohexoses have three stereogenic centers (6-3), hence, eight isomeric forms (Figure 3.2). Those stereoisomers that are non-superimposable mirror images of each other are known as **enantiomers** (or enantioisomers), the rest are called **diastereomers** (or diastereoisomers). Enantiomers have the same physicochemical properties, with the only exception of their optical properties, as they rotate the plane of polarized light in opposite directions. **Epimers** are stereoisomers that differ in the configuration of a single stereogenic center.

The overall configuration of monosaccharides is determined by that of the stereogenic center furthest from the carbonyl group in a Fischer projection: if the hydroxyl group is on the right, the overall configuration is D, otherwise the configuration is L. Most naturally occurring sugars are D (Figure 3.2, Table 3.1). The classical D-L terminology for isomerism preceding the trivial names of monosaccharides (and aminoacids, as we shall see in Chapter 4) is preferred by biochemists over the Cahn–Ingold–Prelog rules [8]. The latter is more systematic, but rather cumbersome for these compounds, thus, the IUPAC systematic name for D-glucose would be (2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanal.

### 3.2.2 Cyclic forms of monosaccharides

Monosaccharides are readily soluble in water due to the presence of hydroxyl groups that form hydrogen bonds with the surrounding water molecules. In aqueous solutions, monosaccharides exist as an equilibrium mixture of acyclic and cyclic forms. In the latter, one of the hydroxyl groups reacts with the carbonyl group

(A)

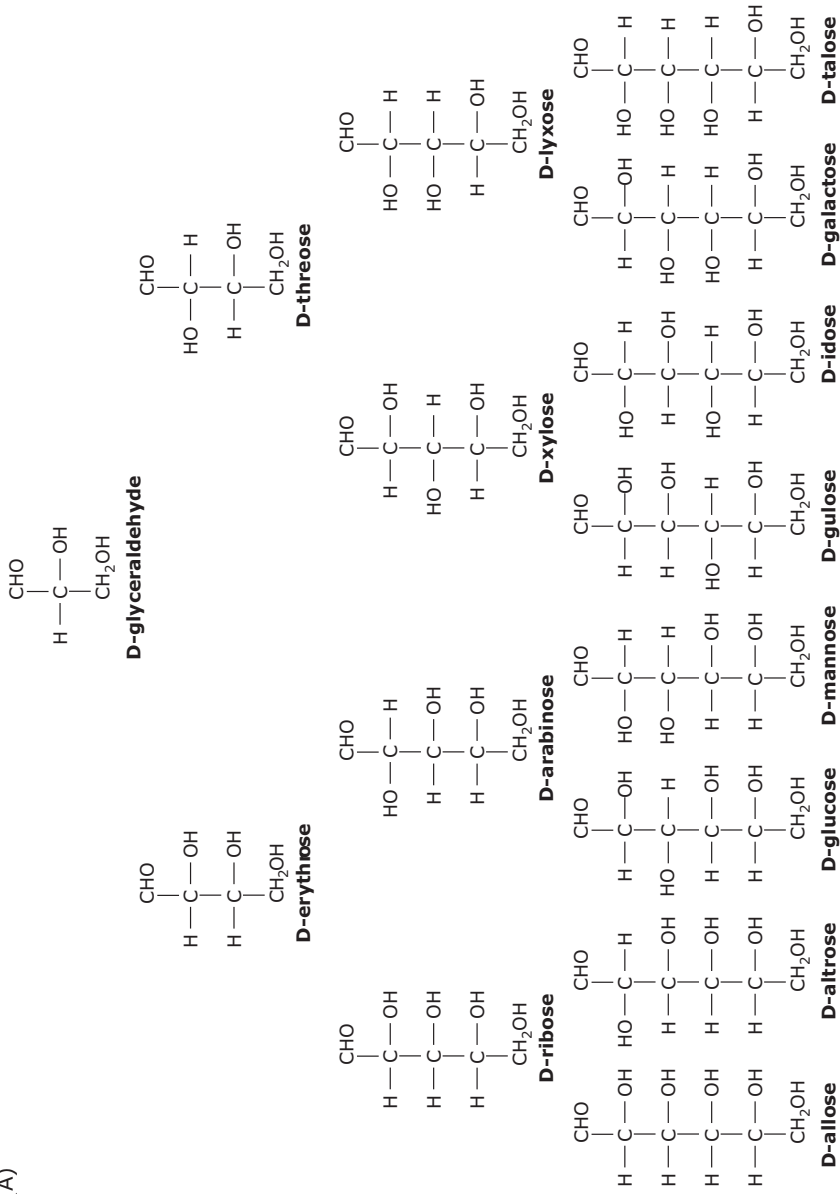
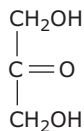
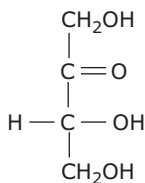
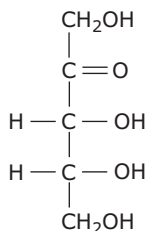
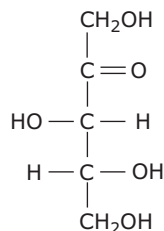
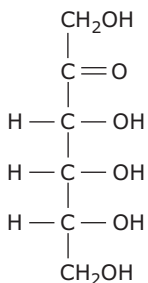
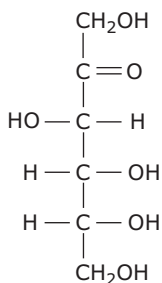
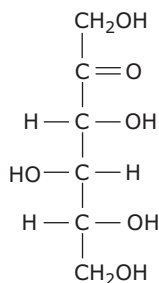
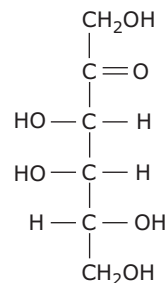
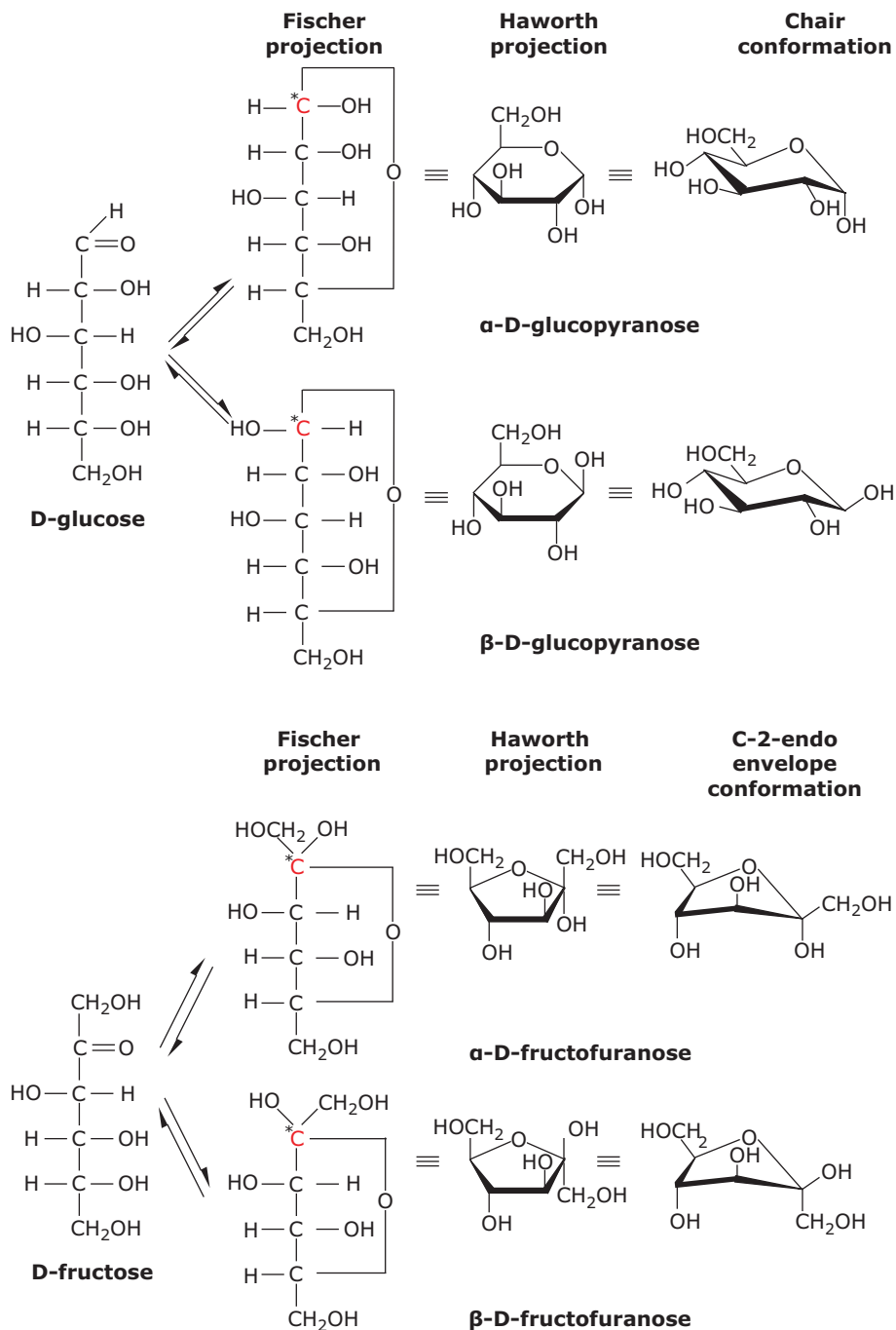


Figure 3.2: The D-aldoses (A) and D-ketoses (B) families of monosaccharides.

(B)

**Dihydroxyacetone****D-erythrulose****D-ribulose****D-xylulose****D-psicose****D-fructose****D-sorbose****D-tagatose****Figure 3.2** (continued)

producing cyclic hemiacetals (Figure 3.3). Five- and six-membered rings are structurally favoured, the former being named furanoses and the latter pyranoses. The formation of cyclic forms in monosaccharides implies the occurrence of a new stereogenic center, known as anomeric carbon, and, consequently, two more stereoisomers named anomers, designated as  $\alpha$  or  $\beta$ . Figure 3.3 shows the anomers resulting of the cyclization of D-glucose in aqueous solution drawn in Fischer and Haworth projections along with their respective chair conformations.



**Figure 3.3:** Formation of the cyclic forms of D-glucose (an aldose) and D-fructose (a ketose). The anomeric carbon is colored in red and marked with an asterisk.

**Table 3.1:** Some monosaccharides of nutritional interest.

Sources	
<b>Pentoses</b>	
L-Arabinose	Plant exudates, hemicelluloses, pectines (dietary fiber)
D-Xylose	Hemicelluloses (dietary fiber)
2-deoxy-D-ribose	DNA
D-ribose	RNA
<b>Aldohexoses</b>	
L-Fucose (6-deoxy-L-galactose)	Human milk, plant exudates, and mucous membranes
<u>D-Galactose</u>	Milk (as lactose), oligo- and polysaccharides, cerebrosides
<u>D-Glucose</u>	Frequent and ubiquitous (sugar, milk, starch, cellulose ...)
D-Mannose	Homo- or heteropolysaccharides, glycoconjugates
<b>Ketohexoses (or hexuloses)</b>	
<u>D-Fructose</u>	Fruits, honey, sacarose

The most abundant in human nutrition are underlined.

For D monosaccharides, the conversion of a Fischer projection into a Haworth projection proceeds as follows:

- The cyclic structure is depicted as a planar ring system with oxygen atom at the top right-hand corner in pyranoses (like glucose) and at the top center in furanoses.
- The numbering of the ring carbons increases in a clockwise direction.
- Groups (–H or –OH) directed to the right in the Fischer structure are given a downward orientation.
- Groups directed to the left in the Fischer structure are given an upward orientation.
- Terminal –CH<sub>2</sub>OH groups are given an upward orientation.

For L sugars, all the steps are the same, but the terminal group is projected downward [6]. The planar Haworth structures are distorted representations of the actual molecules, but they have the advantage of allowing a quick evaluation of stereochemistry around the monosaccharide ring. In 1949, Richard Reeves remodeled the Haworth projection by applying the ring conformations of cyclohexane to describe the structures of the main conformations of pyranoses in solution, leaving the downward or upward orientation of ring substituents unaltered. These conformations were given the names *boat* (B), *chair* (C), *envelope* (E), *half-chair* (H), and *skew* (S). There

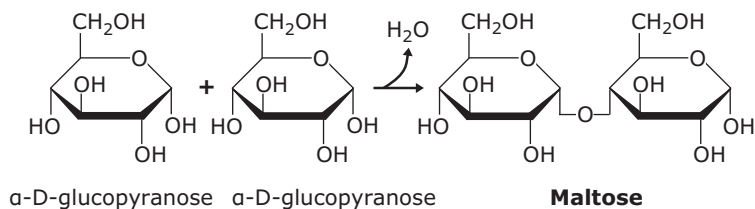
are two C, six B and S, and 12 H and E conformations, making a total of 38 canonical configurations for pyranoses. Most aldohexoses prefer the *chair* conformation [9]. In contrast to pyranoses, furanoses can interconvert between multiple ring conformations (including pyranose rings in chair conformation), complicating the interpretation of structure–function relationships for these molecules [10]. For the sake of simplicity, Haworth projections will normally be used in this Chapter, although ring conformations will be utilized in the formulae of some oligo- and polysaccharides.

Formation and hydrolysis of hemiacetal groups of monosaccharides in aqueous solution result in an equilibrium between cyclic and open-chain forms and even, to a lesser degree, in a mixture of pyranose and furanose forms. When a crystalline sample of a pure anomer is dissolved in water at neutral pH, there is a change in the optical rotation of the solution as the equilibrium between the different anomeric forms is established. This effect is known as mutarotation [9].

Anomerism is extremely important in the biochemistry of carbohydrates because structurally, functionally, and nutritionally different oligo- and polysaccharides are obtained by linking different anomers of the same monosaccharide.

### 3.2.3 Disaccharides and oligosaccharides

A condensation reaction may occur between the anomeric center of one monosaccharide and a hydroxyl group of a second monosaccharide producing a disaccharide and a water molecule (Figure 3.4). The resulting linkage is known as glycosidic bond which can be described in chemical terms as the reaction between a hemiacetal group and an alcohol group to form an acetal [6]. Disaccharides are the simplest oligosaccharides: a new monosaccharidic unit can be linked by means of another glycosidic bond to a disaccharide having a free anomeric hydroxyl group, thus yielding a trisaccharide. This process can be repeated, in theory unlimitedly, to obtain oligo- and polysaccharides.



**Figure 3.4:** Formation of maltose, a disaccharide, from two molecules of  $\alpha$ -D-glucopyranose.

Four disaccharides can be highlighted for their abundance and biological roles: maltose, cellobiose, lactose, and sucrose (Figures 3.4 and 3.5):

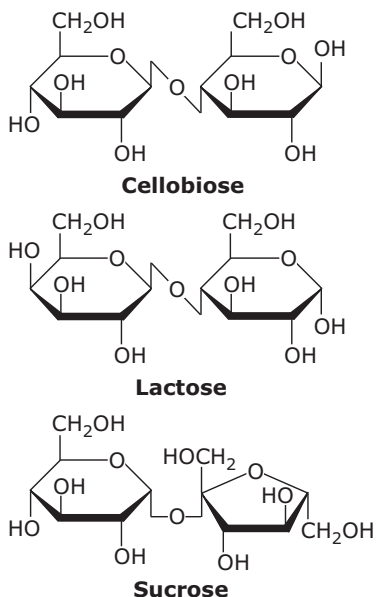


Figure 3.5: Disaccharides of nutritional interest.

- **Maltose** is obtained when a glycosidic bond is formed between the anomeric carbon of a molecule of  $\alpha$ -D-glucopyranose and the C-4 of another D-glucopyranose ( $\alpha$  or  $\beta$ ). This bond is usually denoted as  $\alpha(1\rightarrow4)$  and it is the most abundant glycosidic bond in starch and glycogen, polysaccharides with an important energy store function in many living organisms as we shall see later in this Chapter. The major source of maltose is the enzyme-mediated hydrolysis of starch. The  $\alpha(1\rightarrow4)$  glycosidic bond is readily hydrolyzed during the digestion by specific enzymes (maltase-glucoamylase in the small intestine), consequently, both maltose and starch are good sources of glucose for humans.
- **Cellobiose** is obtained when a glycosidic bond is formed between the anomeric carbon of a molecule of  $\beta$ -D-glucopyranose and the C-4 of another D-glucopyranose ( $\alpha$  or  $\beta$ ). This bond, denoted as  $\beta(1\rightarrow4)$ , is present in cellulose, the most abundant biomolecule on the Biosphere that performs an important structural function in plants and some bacteria (see below).
- **Lactose** is the principal sugar of mammals' milk. In human milk, lactose concentration varies between 6.4 and 7.6 g/dL [11]. This disaccharide results from the formation of a glycosidic bond between the anomeric carbon of a  $\beta$ -D-galactopyranose and the C-4 of a D-glucopyranose [ $\beta(1\rightarrow4)$  glycosidic bond]. It is hydrolyzed by lactase (also known as lactose galactohydrolase and lactase-phlorizin hydrolase, EC 3.2.1.108), a membrane-associated glycoprotein located at the brush border of enterocytes, the absorptive cells located at the small intestine epithelium. Insufficient levels of lactase activity cause the accumulation of lactose in the bowels, triggering a number of symptoms known

as **lactose intolerance**, one of the most common digestive problems in humans [12] (see below).

- **Sucrose** results from the linking of the anomeric carbons of a  $\alpha$ -D-glucopyranose (C-1) and a  $\beta$ -D-fructofuranose (C-2) with a glycosidic bond. It is a major product of plant photosynthesis, playing important biological roles in growth, development, and storage among others [13]. It is also the most common, almost universal, sweetener, being industrially obtained from sugar cane in tropical and sub-tropical countries, and from sugar-beet in temperate zones. Although competition is increasing from alternative and synthetic sweeteners, worldwide production of sugar in 2017 was around 180 million metric tones and it is expected to rise steadily up to more than 200 million metric tones in the next decade [14]. The glycosidic bond of sucrose is hydrolyzed by the enzyme sucrase-isomaltase (EC 3.2.1.48), expressed in the human intestinal brush border, and also by extracellular invertases (or  $\beta$ -D-fructofuranosidases, EC 3.2.1.26) present in the microbial flora of the oral cavity [15]. Mutations in the gene coding for the human sucrase-isomaltase are the cause of congenital sucrase-isomaltase deficiency, a rare disease that has been linked to irritable bowel syndrome [16].

Maltose, cellobiose, and lactose have two anomeric carbons (one per participating monosaccharide), one of them being involved in the glycosidic bond. In aqueous solutions, hydrolysis of the other hemiacetal group allows the presence of cyclic structures with different configurations as well as an acyclic structure bearing an aldehyde group. As a consequence, these disaccharides exhibit mutarotation and participate in oxidation and reduction reactions through the carbonyl group, being considered reducing sugars. Sucrose, on the contrary, does not show these properties because both anomeric carbons become “fixed” due to their participation in the glycosidic bond. Consequently, sucrose is a non-reducing sugar.

### 3.2.4 Derivatives of monosaccharides

Although monosaccharides are in principle composed of carbon, hydrogen, and oxygen atoms linked according to the basic formula  $(\text{CH}_2\text{O})_n$ , a high number of derivatives of these substances occur in living organisms (Figure 3.6). Among these are:

- **Aminosugars:** Monosaccharides in which a hydroxyl ( $-\text{OH}$ ) group is replaced with an amine group ( $-\text{NH}_2$ ), most commonly at the C-2 of aldoses, yielding 2-amino-2-deoxy sugars
- **Deoxysugars:** Monosaccharides in which a hydroxyl group is replaced with a hydrogen atom. The most important member of these derivatives is 2-deoxy-D-ribose, a component of the deoxyribonucleic acid (DNA).
- **Acidic sugars:** the aldehyde group ( $-\text{CHO}$ ) and/or the hydroxymethyl group ( $-\text{CH}_2\text{OH}$ ) at the other end can be oxidized to a carboxyl group ( $-\text{COOH}$ ). Three

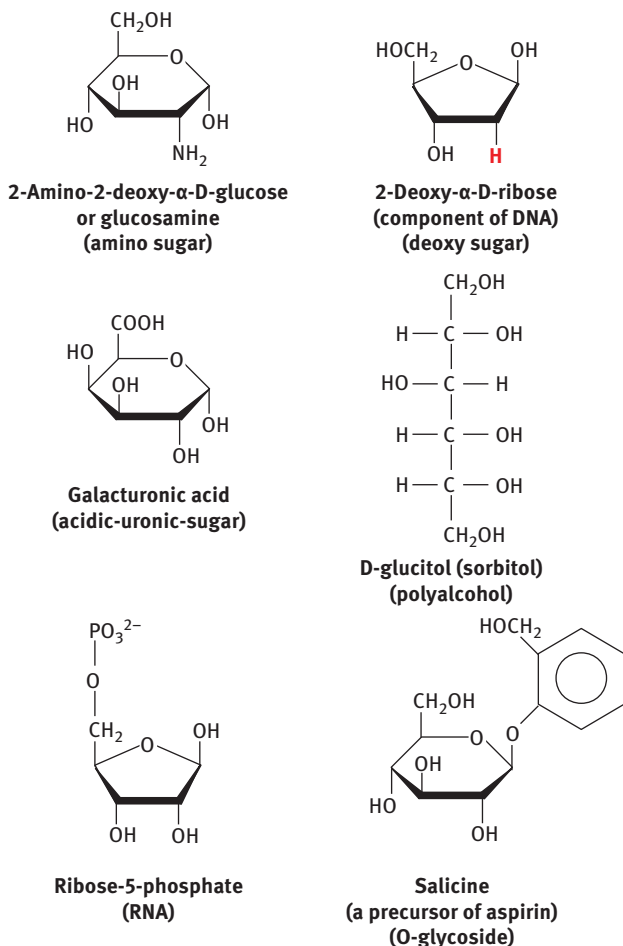


Figure 3.6: Some derivatives of monosaccharides.

types of acidic sugars can be obtained depending on the location of the carboxyl group: **aldonic** (at the C-1), **uronic** (at the last carbon), and **aldaric** (two  $\text{-COOH}$  groups at both ends of the carbon backbone) acids.

- **Polyalcohols (alditols):** Polyhydroxylated derivatives resulting from the replacement of a carbonyl group with a  $\text{CHOH}$  group.
- **Esterified sugars:** an acid can react with one of the hydroxyl groups of the monosaccharide molecule producing an ester derivative.
- **Glycosides:** Monosaccharides (or oligosaccharides) bound to a non-carbohydrate moiety (known as **aglycone**) by glycosidic bonds. There are several types of glycosides depending on the type of bond established between the sugar and the aglycone:

- **O-glycosides** are usually formed when the –OH of the hemiacetal group of a monosaccharide (or a oligosaccharide) reacts with an aliphatic or aromatic alcohol through a nucleophilic substitution reaction that results in a bond between the two moieties through an oxygen atom and a loss of a water molecule. This type of link is present in *O*-linked glycoproteins. Other interesting examples of *O*-glucosides are steviol glycosides, a group of highly sweet diterpene glycosides discovered in plant species such as *Stevia rebaudiana* and others that are becoming increasingly popular as sweeteners [17]. “Cardiac glucosides” are also a family of *O*-glycosides in which the aglycones are sterol derivatives. They are found in plants like *Digitalis purpurea* and include molecules (digitonin, ouabain . . .) with strong pharmacologic activities in conditions such as congestive heart failure or cancer [18].
- **N-glycosides** are generated when the sugar component is attached to the aglycon, through a nitrogen atom, establishing as a result a C-N-C linkage. Nucleosides, essential components of nucleic acids, are *N*-glycosides of ribose or 2-deoxy-ribose as the sugar and a purine or a pyrimidine as the aglycon. The C-N-C linkage is also present in *N*-linked glycoproteins.
- In **C-glycosides**, the anomeric center of the sugar moiety is linked to the aglycone by means of a carbon–carbon bond. *C*-glycosides occur in microbes, plants, and insects, where they serve a diverse range of functions. In plants, the most abundant *C*-glycosylated products are the flavonoids, a large group of polyphenolic compounds. From a dietary perspective, these compounds have been suggested to have both positive and negative biological activities [19].
- In **S-glycosides**, the sugar moiety is attached to a sulfur atom of the aglycone. Glucosinolates are an example of S- $\beta$ -glucosides present primarily in the species of the order Brassicales (that include mustard, cabbage or horseradish) that release toxic chemicals like nitriles, isothiocyanates, epithionitriles, and thiocyanates in reactions catalyzed by thioglucosidases. This mechanism is believed to be part of the plant’s defense against insects and pathogens [20].

## 3.3 Vitamin C

### 3.3.1 Properties and biosynthesis

Vitamin C, or L-ascorbic acid, is a monosaccharide derivative first identified in the 1920s by Albert von Szent Györgyi as a chemical compound that could prevent and cure scurvy. A decade earlier, Casimir Funk (1884–1967) had attributed scurvy, pellagra, rickets, and beriberi to nutritional deficiencies of certain factors that he called “vitamins.” Vitamin C was the name proposed for the unidentified anti-scurvy factor [21, 22]. Scurvy is a potentially life-threatening condition, already