Chapter 5
Molecular Approaches to Explore Natural and Food-Compound Modulators in Cancer Epigenetics and Metabolism

Alberto Del Rio and Fernando B. Da Costa

5.1 Introduction

Let food be thy medicine and medicine be thy food (Hippocrates)

The biological activity of chemical constituents from natural sources and food is crucial in many cellular processes. Several clinical, physiopathological, and epidemiological studies highlight the detrimental or beneficial role of natural/food factors in conjunction with epigenetic and metabolic alterations. Chemical constituents isolated from various sources can interfere with many different biological targets and have been considered as possible starting points for therapeutic purposes. These agents include, for example, curcumin (turmeric), genistein (soybean), polyphenols (green tea, berries, and cocoa), resveratrol (grapes), and sulforaphane (cruciferous vegetables). Moreover, a wide variety of compounds from medicinal plants, spices, bees, or fish can also be mentioned as examples in this category. Among pathways and functions of cells that are notably modulated by these natural constituents, metabolism and epigenetics have emerged in the context of cancer prevention and therapy. Interestingly, epigenetic changes are tightly linked to metabolism, thus adding a higher level of complexity to elucidate the biological role of these compounds. A deeper understanding on how metabolism and epigenetics are influenced by compounds from natural sources and food can be achieved at molecular level by using a variety of chemoinformatic and computer-aided techniques. These include data mining, molecular databasing, and molecular design techniques such as

A. Del Rio (✉)
Institute of Organic Synthesis and Photoreactivity (ISOF), National Research Council (CNR), Via P. Gobetti 101, 40129 Bologna, Italy
e-mail: alberto.delrio@gmail.com, alberto.delrio@isof.cnr.it

Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Alma Mater Studiorum, University of Bologna, Via S.Giacomo 14, 40126 Bologna, Italy

F. B. Da Costa
School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Avenida do Café s/n, Ribeirão Preto, SP 14040-903, Brazil

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pharmacophore-based methods or molecular docking. An overview of these techniques will be described in this chapter in the view of using them as valuable tools to elucidate molecular determinants, mechanism of actions, and polypharmacological role of chemical constituents of food and natural sources.

5.2 Bioactivity of Natural and Food Compounds

The idea that nature is a rich source of bioactive constituents is a 4000-year-old concept. Indians, Egyptians, and Chinese have used natural sources as medicines in early periods of the human civilization. Hippocrates often described diet as a valuable way to treat diseases such as diabetes. Dioscorides, in his five-volume encyclopedia, described the medical uses of herbs, animals, and minerals, and this fantastic work remained alive for more than 15 centuries. Today, lifestyle modifications based on healthy diet, thus on the intake of food and natural compounds, is called lifestyle medicine. The perception that bioactivity of nutraceuticals may have causal relations with the cure or treatment of diseases and, therefore, influence the biological balance of our organism, was spurred starting from the early 1900s. A valuable example of this concept is the treatment of goiter, a disease caused, for over the 90% of cases, by an iodine deficiency, successfully carried out by the administration of iodine-rich foods or potassium iodine. Yet, the beneficial role of natural compounds has been progressively associated to specific food intake. For instance, it has been observed that consuming fish could contribute to keep in good health heart of healthy people as well as positively influence people who are affected by cardiovascular diseases and are exposed to correlated risks. Thanks to the progress in the analytical techniques of food chemicals, fish was identified to be a good source of omega-3 fatty acids (Fig. 5.1a). Indeed, this class of compounds has the capacity to decrease the risks of arrhythmia, triglycerides level, the rate of atherosclerotic plaque, and to lower blood pressure. Consequently, the beneficial effects of fish have been linked to omega-3 fatty acids.

The awareness that natural compounds and food have beneficial or detrimental effects on our life has been also fuelled by the growing epidemiological evidences that have been made possible by the effective exchange of scientific data, the growing availability of specific natural sources, and the effective number of scientists dedicated to the study of phytochemicals, e.g., in the field of pharmacognosy. This kind of research has also assumed in the past decades the "multidisciplinary" dimension involving not only pharmacists, chemists, and pharmacologists but also biochemists, cellular and molecular biologists, toxicologists, and clinicians, among others. Despite the growing information about natural and food components that would suggest their usage as valuable chemicals to prevent and/or treat diseases, contributing to people well-being, there are still several hurdles to clear in this field pervaded by misinformation, not only in the scientific literature but also in the common knowledge. For instance, a common misconception is the assumption that "natural

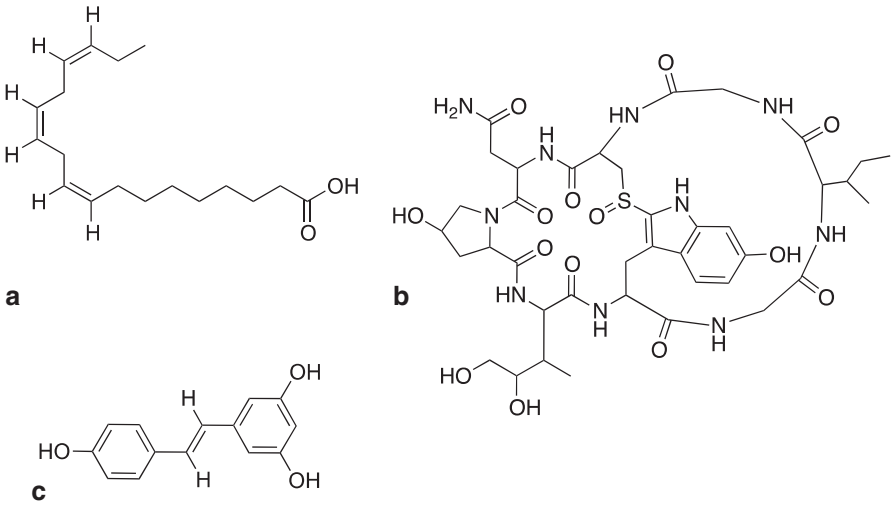

Fig. 5.1 Chemical structures reporting examples of natural compounds with different biological effects. **a** α-Linolenic acid, an essential omega-3 fatty acid. Omega-3 is known to decrease the risk of cardiovascular diseases; **b** α-amantine is a deadly natural compound found in the *Amanita phalloides* mushrooms; **c** resveratrol, a polyphenolic stilbenoid produced in plants with several reported pharmacological actions

is always good," which is an easily falsifiable statement. Indeed, a large number of phytochemicals are known to be harmful for health and, in several cases, also lethal. For example, α-amantine (Fig. 5.1b) is a natural cyclic octapeptide contained in the *Amanita phalloides* fungus, which is widely distributed across Europe and resembles several species of edible mushrooms. α-Amantine is an example of highly poisonous and deadly natural compound which was proved to bind to the bridge helix in RNA polymerase II, interfering with the translocation of RNA and DNA, leading to a drastically reduced rate of synthesis of the RNA molecule [1]. There are numerous classical examples of natural constituents from plants or food which are dangerous to health, such as strychnine from *Strychnos* species, cyanogenic glucosides from cassava (*Manihot* species) or myristicin from nutmeg (*Myristica fragrans*).

To clarify the role of natural and dietary compounds, an elucidation of the interaction mechanisms of these molecules with the human biological network is required, especially at a molecular level. This includes the uncover of the biophysical mechanisms by which these compounds bind to receptors or enzymes (i.e., allosteric regulation and inhibition/activation profile) and their kinetics (i.e., reversible/irreversible, substrate and cofactors competition/non-competition) that could underlie to specific pharmacological actions. These studies are far to be accomplished because, in many cases, it is experimentally difficult to isolate large amounts of compounds from the natural source and, even when this is possible, it is complicated to dissect their intrinsically polypharmacological roles, rendering this area of research

extremely challenging. An exemplifying case of polypharmacology is resveratrol (Fig. 5.1c), a polyphenolic stilbenoid produced in plants and found in wine which possesses several reported pharmacological actions, including anti-inflammatory, anticarcinogenic, antimutagenic, antiaging, antioxidant, and anticoagulant. Many examples reporting bioactivity of resveratrol in different molecular pathways can be found in the literature [2–6].

5.2.1 Pharmaceutical Development of Natural Compounds

It was only after the advent of advanced technologies for isolation, purification, and structure elucidation of organic compounds that scientists could realize how natural sources were able to deliver an important amount of diverse chemical entities. Nowadays, it is well known that the natural product landscape constitute a very varied supply of building blocks and intermediates useful for the drug discovery process, which, in many cases, represent the starting point for generating lead compounds. The latter can be further synthetically modified in order to create and develop specific therapeutically relevant pharmaceuticals [7]. The impressive chemical diversity along with the structural complexity of natural compounds represents a source of inspiration for the generation of chemical libraries belonging, in most cases, to an unexplored and "intellectual property free" chemical space, allowing pharmaceutical companies to protect composition of matter together with medical uses [8]. In this sense, we assist to a conceptual shift, passing from the classical era of combinatorial chemistry, during which pharmaceutical companies essentially disregarded the development of natural products as potential drug candidates, to the development of targeted or focused compound libraries inspired by natural sources [9]. The accumulating evidence that the natural selection process represents a unique way to diversify the chemistry of natural compounds and the way in which the latter evolved in biological organisms has favored this process. For these reasons, the interactions of natural compounds with other biological macromolecules reflect, in different cases, high specificity and potency profiles. Since natural products can be considered the richest source of novel chemical scaffolds for biological studies, technologies and strategies to extract them from different sources have evolved rapidly in the past years [10]. A number of advanced separation and structure elucidation techniques are now available for chemists/pharmacists that can now have access to an increasing number of purified natural compounds [11]. Among the separation procedures, high-performance liquid chromatography (HPLC) is the technique of choice because it allows isolation of compounds from the analytical to the preparative scale level. In addition, HPLC can also be coupled to ultraviolet (UV), mass spectrometry (MS), or nuclear magnetic resonance (NMR), comprising the so-called hyphenated or tandem techniques (LC-MS or LC-NMR), which greatly increase the efficiency of compound identification [11].

However, despite the advance in purification techniques, natural products resources are still largely unexplored, mostly due to the technical obstacles to collect

samples, especially from the most concealed places on earth, e.g., deep sea level, arid or extremely cold regions. Historically, the most widely used natural compounds have been isolated from plants and animals by means of classical chromatographic techniques such as column or thin-layer chromatography. Subsequently, cultured soil microorganisms, or the direct access to the genome of soil organisms clonable into culturable organisms, provided a rich source of natural products [12]. In the last decade, compounds recovered from the marine environment have come into focus: Indeed, oceans harbor one of the widest variety of ecosystems on earth, a fact reasonably reflected by an unprecedented discovery of new chemical entities of marine origin.

Food compounds, most of them plant secondary metabolites, can be seen as a particular class of natural compounds since they have to be considered as materials designated as "generally recognized as safe" (GRAS) [13]. There is currently a great deal of interest in exploring benefits of bioactive food components and relate them to health and wellness. However, despite the efforts made by researchers to identify food-compounds, few studies report the systematic extraction and purification of a specific bioactive component from different food sources, with the notable exceptions of fruits, vegetables, beverages, and essential oils [14, 15].

5.2.2 Anticancer Compounds from Natural and Food Sources

Natural and dietary compounds present molecular scaffolds that are particularly attracting as sources of lead compounds for cancer therapy. Indeed, more than 60% of the anticancer drugs have natural origin or are the result of chemical optimizations of natural scaffolds. Accordingly, it is not surprising that the interest in natural products have gained momentum in the past years, as their application as lead compounds is source of novel chemical entities (NCEs) in different areas of anticancer drug design [16–18]. With their unique chemical diversity, the usage of natural compounds in cancer therapies is even more justified if considered the wide range of variability in terms of biochemical and biological pathways that are present in cancer pathologies. The result of the drift toward natural compounds and their derivatives is reflected by the wide range of chemical compounds from very different sources already associated to bioactivities of oncogenic targets.

Historically, this discovery resulted mainly in the development of anticancer agents from plants (e.g., vinca alkaloids like vincristine and vinblastine; *Podophyllum* lignans like podophyllotoxin; taxanes like paclitaxel and docetaxel; and quinoline alkaloid like camptothecin, topotecan, and irinotecan), marine organisms (i.e., toxins like latrunculins; didemnins like aplidine and trabectedin; and strongylophorines) and microorganisms (e.g., anthracyclines like doxorubicin, daunorubicin, mitoxantrone and idarubicin; chromomycins like dactinomycin and plicamycin; and miscellaneous antibiotics like mitomycin and bleomycin). More recently, different types of terpenoids have been demonstrated to inhibit the NF-kB signaling, to suppress inflammation processes and to reduce cancer progression

[19] while α-methylene-γ-lactones, in particular sesquiterpene lactones (especially found in Asteraceae species), have proven to be promising candidates for treatment of various types of cancer [20–22]. Salinosporamides, a class of marine natural compounds, present in *Salinispora tropica* bacterium, were identified to be potent inhibitors of proteasome [23].

Among natural sources, several food-component agents have also been identified as beneficial for anticancer therapy. Dietary sources including fruits, vegetables, and spices have drawn a great deal of attention from the scientific community due to their demonstrated ability to interfere with cancer mechanisms; nevertheless, speculations by the general public has fomented the idea that fabricated supplements can be a panacea [24]. Scientific literature provided evidence that the regular consumption of fruits, vegetables and spices lowers the incidence of cancers (i.e., stomach, esophagus, lung, oral, endometrium, pancreas, and colon) [25]. These agents include curcumin (turmeric), resveratrol (red grapes, peanuts and berries), genistein (soybean), diallylsulfide (allium), *S*-allyl cysteine (allium), allicin (garlic), lycopene (tomato), capsaicin (red chili), diosgenin (fenugreek), 6-gingerol (ginger), ellagic acid (pomegranate), ursolic acid (apple, pears, prunes), silymarin (milk thistle), anethol (anise, camphor, and fennel), catechins (green and white tea, berries and cocoa), eugenol (cloves), indole-3-carbinol (cruciferous vegetables), limonene (citrus fruits), beta-carotene (carrots), and several dietary fibers.

Many other examples of natural and dietary compounds that have a role in cancer-related diseases underline the importance of this topic in oncological research. In the following paragraphs, we provide an overview of these compounds that specifically modulate cell pathways and functions connected to epigenetic and metabolic changes in cancer diseases.

5.3 Epigenetic and Metabolic Pathophysiology of Cancer

Cancer is a complex set of diseases. Genetic aberrations, epigenetic alterations, and inflammations constitute some of the known mechanisms by which normal cells develop and progress towards neoplastic pathologies. While last decades marked a major understating in cancer genetics, it is now evident that the dissection of the mechanisms of this multifaceted set of diseases requires a deeper look in other paradigms of cancer biology in order to conceive new prevention or therapeutic approaches. This larger framework has evolved in the recent years on novel lines of research, for instance, toward the understanding of the immune system regulation [26, 27] and the epigenetic modifications, but also on the reinterpretation of old studies by means of new scientific awareness that marked a return to cancer metabolism [28–31]. In the next paragraphs, we will discuss cancer metabolism and epigenetics, focusing on the possibilities to interfere with the mechanism of pathogenesis and progression of cancer diseases by means of small molecules of natural and food origin.

5.3.1 Natural Compounds Modulating Epigenetic and Metabolic Mechanisms

Epigenetics is a general term that refers to modifications of genes expression through alteration of chromatin structure and/or DNA methylation occurring without changes in the DNA sequence, from which the term *epi*-(from greek: over, outside of, around)*genetics*. Global modifications of chromatin packaging and its influence in the transcription of associated genes fuelled the research on cancer epigenetics in the past years. The ensemble of known epigenetic mechanisms can be categorized into three classes: i) histone posttranslational modifications (PTMs) that represent one of the major way to arrange the different states of chromatin; ii) DNA methylation, i.e., the methylation of DNA cytosines to 5-methylcytosines; and iii) regulation of gene expression by non-coding RNA (ncRNA). The elucidation of epigenetic phenomena, representing nowadays an important topic of research, is necessary to understand the basis of several biological processes and is progressively translating into the development of new therapeutic *epi-compounds* or *epi-drugs* [32–34]. Different studies have highlighted how alterations in the epigenetic code contribute to the onset and growth of a variety of cancers [35–48]. Consequently, epigenetic modifications are constituting attractive therapeutic targets for the development of new cancer therapies [33, 49–52]. An increasing number of reports describe, in particular, new types of histone post-translational modifications (PTMs) associated with the characterization of the enzymes that are in charge of operating these chemical reactions [53]. Yet, other studies point on the validation of these PTMs in the context of chromatin remodeling and regulation, as well as their clinicopathological relevance in human diseases [54]. It is important to point out that the increasing evidences linking epigenetic targets and cancer pathologies have been boosted by the surge of structural data describing these proteins, thus creating the basis to develop specific probe compounds and start new drug discovery campaigns [54, 55]. However, although the ensemble of these data promises to shed light on cancer epigenetics, the way in which epigenetic modifications relate to cancer and, consequently, their therapeutic relevance in cancer diseases, is still largely unknown. Most of these targets, despite being linked to cancer pathologies, may not have causal role in specific malignant transformations. Some notable exceptions [56, 57] are the recent success stories documenting the potential to interfere with these mechanisms by means of small organic molecules [34]. In particular, the first clinical results have been obtained with histone deacetylases (class I, II and IV HDACs) inhibitors [58], DNA methyltransferases inhibitors (DNMTi) [59] and histone methyltransferases inhibitors [60]. Other classes of epigenetic enzymes are rapidly reaching the potential to become pharmaceutically validated biological targets. Among them are sirtuins, which are NAD^+-dependent histone deacetylases also known as class III HDACs [6], and histone demethylases [61]. Apart from histones PTMs and DNA methylation, growing evidences indicate that modulating microRNAs expression might be useful to interfere with epigenetic mechanisms and develop novel RNA-based drugs for a wide range of diseases [62–65]. Indeed,

the deregulation of microRNAs expression and activity is frequently observed in a variety of human pathologies including cancer [66]. Therefore, in addition to the general strategy of increasing or decreasing miRNA abundance and activity by using oligonucleotides or plasmid- and virus-based constructs, a novel paradigm aims to target miRNA expression by means of specific compounds targeting miRNA transcription and processing. Clearly, the potential success of small molecules can be ascribed to their capacity to circumvent the issue of delivery into most tissues making them very attractive as a therapeutic tool.

Metabolic changes have been rediscovered in the context of cancer diseases after the initial observations of Otto Warburg in the early 1920s [30, 31, 67]. Warburg noticed that proliferating cancer cells consume glucose at a high rate, releasing lactate and not carbon dioxide. Indeed, one of the primary metabolic changes in cancer transformation is constituted by an increased catabolic glucose metabolism characterized by high rates of anaerobic glycolysis, regardless of oxygen concentration. While the underlying mechanisms that alter metabolic programs of cancer cells are still to be fully elucidated, it is known that several genetic alterations in cell pathways responsible for the regulation of cells metabolism contribute to cancer growth and progression. For instance, the conversion of glucose to glucose-6-phosphate (G6P) is critical to different cancer phenotypes, a process catalyzed by the enzyme hexokinase-II. Thus, intermediates of glycolysis like G6P can therefore accumulate, creating a highly advantageous environment for cancer survival and growth. On these bases, the pharmacological modulation of specific metabolic enzymes is currently under investigation by various research groups as a viable strategy to block cancer cell proliferation [68–72].

Several natural and dietary components have been already identified as capable to interfere with different epigenetic and metabolic mechanisms [29, 73, 74] (Fig. 5.2). Dietary components like phenolics from green tea, genistein from soybean, isothiocyanates from plant foods (e.g., from Brassicaceae species), diallylsulfide from garlic, curcumin from turmeric, resveratrol from grapes, and sulforaphane from cruciferous vegetables have been studied for their ability to target the epigenome, in relation, for instance, to breast cancer [73, 75–79]. While in most of the cases the mechanisms of action of natural compounds are still poorly understood, some of them have been identified. For instance, luteolin (Fig. 5.2), a common flavonoid found in parsley and celery has been demonstrated to inhibit DNMTs and sirtuins (SIRTs), while retinoic acid, found in carrots, spinach and eggs, and used nowadays to treat leukemias, is an HDAC inhibitor. Among polyphenols, epigallocatechin-3-gallate, the major compound found in green tea, was reported to have a complex polypharmacology, as inhibitor of histone acetyltransferases (HATs), HDACs, SIRTs, DNMTs, retinoic acid receptor (RARβ), proteasome, 78 kDa glucose regulated protein (Grp78) and heat shock protein 90 (Hsp90). Similarly, curcumin (Fig. 5.2) and curcuminoids have also been widely studied for their anti-inflammatory, antiangiogenic, antioxidant, wound healing, and anticancer effects. Importantly, curcumin analogs, like dihydrocoumarins, have been demonstrated to inhibit sirtuins. Since the isoform SIRT1 has been shown to have a role in deacetylating p53, a master regulator of metabolic function in the cell, the inhibition of enzymes like SIRT1 likely contributes to the

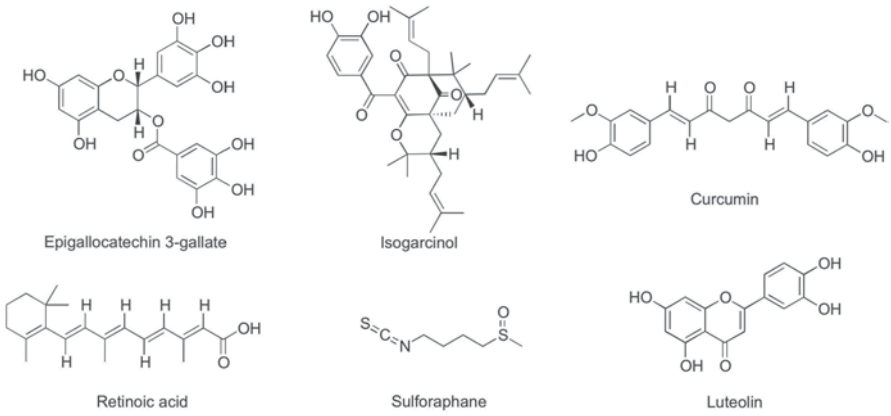

Fig. 5.2 Examples of the chemical diversity of natural compounds with a role in epigenetics and metabolic pathways

regulation of both epigenetic mechanisms and metabolic pathways like glycolysis. Other classes of natural compounds, such as anacardic acid and related compounds from cashew nut, alkaloids such as sanguinarine, quinone derivatives, peptides and peptide conjugates, and polyisoprenylated benzophenone derivatives (PBDs), have been demonstrated to have activities against HATs [80]. As previously pointed out, the discovery of natural scaffolds is allowing the development of focused libraries of compounds that are able to act on epigenetic enzymes with more potent and specific profiles. An example of this strategy is given by Kundu and co-workers, who could generate garcinol derivatives starting from isogarcinol (Fig. 5.2), in order to develop inhibitors for p300 and PCAF HATs [81]. Because of the tight connection with epigenetic and metabolic changes, it is known that specific cancer conditions are strongly influenced by lifestyle and environmental factors, including the intake of food and nutrients [82]. For instance, the absorption of compounds like flavonoids and folates through diet has been shown to alter DNA methylation and modify the risk of human colon cancer and cardiovascular diseases, even though their mechanisms of action have to be ascertained, yet [83–85]. Additional researches on the effects that nutraceuticals have on epigenetic and metabolic changes promise to be relevant for devising new preventive and therapeutic interventions.

5.3.2 Linking Metabolism and Epigenetic Mechanism

Growing evidences show how epigenetic changes are linked to cancer metabolism in different cancer pathologies [29]. It is meaningful to stress on how many enzymes, substrates, and co-factors are common in metabolic and epigenetic pathways/targets, as shown in Fig. 5.3. For example, sirtuins deacetylate histone proteins and have also a primary role in metabolic regulation which is dependent on the pool of intracellular NAD^+, whose biosynthesis and signaling became an emerging area in

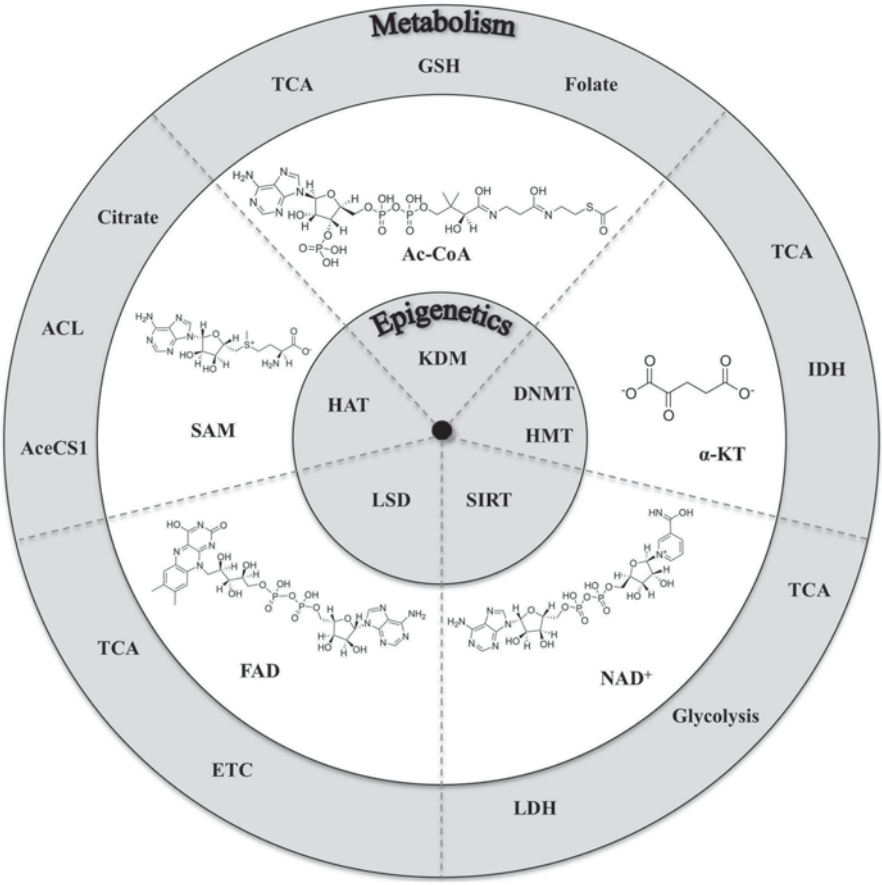

Fig. 5.3 Examples of connections between epigenetics and metabolic pathways. (Abbreviations: *α-KT* α-ketoglutarate; *AcCoA* acetyl coenzyme A; *AcsCS1* acetyl-CoA synthase 1; *ACL* ATP-citrate lyase; *ETC* electron-transport chain; *FAD* flavin adenine dinucleotide; *GSH* glutathione; *IDH* isocitrate dehydrogenase; *LDH* lactate dehydrogenase; *NAD*$^+$ nicotinamide adenine dinucleotide; *SAM S*-adenosyl methionine; *TCA* tricarboxylic acid cycle)

medicinal chemistry [86]. Many cancer cells rely on glycolysis to satisfy their energy requirements, a process that leads to the production of lactate and not of acetyl-CoA (AcCoA), like for healthy cells. Since AcCoA is also a substrate of epigenetic enzymes, such as histone acetyltransferases (HATs), depletion of the AcCoA in cancer cells might contribute to epigenetic alterations. A similar consideration can be drawn for other metabolic co-substrate and co-factors like *S*-adenosylmethionine (SAM), flavin adenine dinucleotide (FAD), and α-ketoglutarate (Fig. 5.3), which are all involved in the epigenetic regulation through various enzymatic mechanisms [87]. Moreover, compounds of natural and food origin can be converted by cell

metabolites into chemical intermediates implicated in epigenetic and metabolic alterations [25, 29, 44, 75, 82, 88]. So, it is evident that a molecular-level knowledge of the connections between metabolism and epigenetic mechanisms is required in order to define the polypharmacological role of small molecules. It should be noted that the biological effect of many chemical scaffolds, especially of natural origin, is in most cases ascribable to a promiscuous activity towards biological targets that uses common substrates and cofactors like NAD+/NADH, FAD, SAM, AcCoA, α-ketoglutarate, and ATP. Therefore, in the framework of developing compound libraries from natural and food origin, it is essential to assess compounds against their impact on epigenome and metabolism by looking at their polypharmacological behavior. In particular, the screening of biological activities acquires importance if considered that the detrimental or beneficial effects of natural compounds for the treatment of a specific disease, is dependent on the physiopathological context [89].

5.4 Computer-Aided Molecular Design Approaches

Computer-aided molecular techniques are heavily used in academia and industrial settings to assist the selection of new compounds with predefined biological activity. Several examples testify their successful applications in the development of new chemical entities [90–92] and a wide range of disciplines nowadays revolve around computer-aided drug discovery (CADD), including chemoinformatics, computational chemistry, structural biology, biophysics, medicinal chemistry, organic chemistry, and pharmacology. Among the various computational techniques available, virtual screening is certainly the most popular to screen rapidly and cost-effectively new chemicals from large libraries of compounds [93–95]. In principle, this technique can be divided in ligand- and structure-based drug design techniques (LBDD and SBDD): the first category usually takes advantage of information from known bioactive compounds (ligand), while the second usually exploit three-dimensional structure of the biological target (protein) in order to identify putative modulators of the protein activity. In the past years, the growing availability of protein structures, resolved by structural biologists, progressively raised the possibility to deploy SBDD. Nevertheless, ligand-based techniques are still essential tools, for example when structural information of a biological target is missing or when the molecular design is not directed towards a target-centric approach, but point to modulate cellular pathways or phenotypic traits without a precise knowledge of the mechanism of action. In addition, it should be noted that, despite the apparent advantage and the success of the target-centric approach, which consist in the design of small molecules having high-selectivity profiles against a specific target, it has failed in many other cases [96].

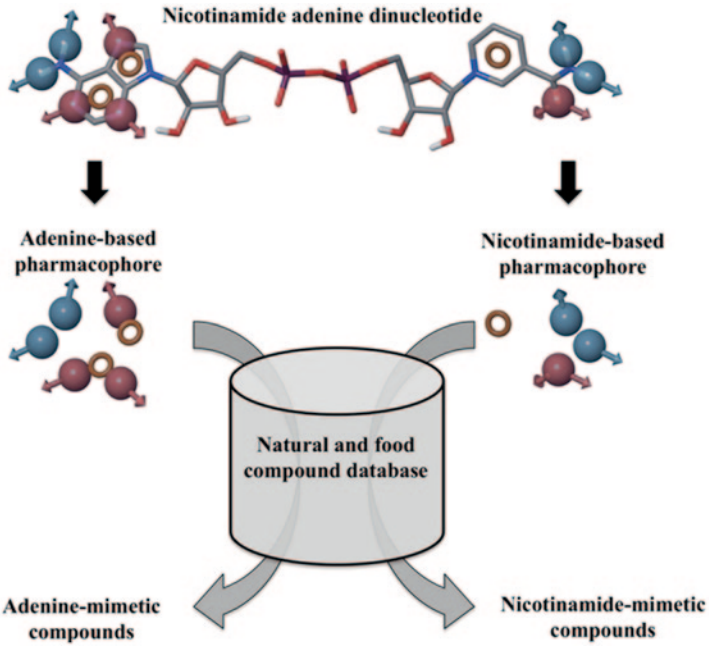

Fig. 5.4 Example of pharmacophore-based *in silico* approach to discover adenine and nicotinamide mimetic compound of NAD^+ originating from natural or food sources

5.4.1 CADD Approaches on Epigenetic and Metabolic Targets

As seen in previous sections, the research aiming at developing new therapeutic anticancer strategies against epigenetic and metabolic targets has flourished in the past years. Several reports describe rationales, targets, new drugs, approaches, novel compounds, and methodologies [34, 35, 37, 41–48, 52, 53, 56, 97–107]. Computational techniques are being actively used in this field and several reviews and articles have been published recently on this topic [56, 57, 59, 105, 108, 109]. A valuable example is the extensive usage of computer-aided techniques for epigenetic enzymes like sirtuins [6, 108, 110–114]. A variety of computational tools like molecular docking and pharmacophore mapping have been used to identify novel modulating compounds while trying to explain the mechanism of actions of these small molecules. Equally, theoretical tools have also been applied to identify and elucidate pharmacological mechanisms of metabolic enzymes like lactate dehydrogenase and hexokinase-II [69, 114, 115]. Of note, many of these targets use NAD^+ as a cofactor and several computational strategies were directed to find competitive compounds of either the adenine or the nicotinamide pocket, or both. As an example, Fig. 5.4 depicts a typical *in silico* screening workflow that uses pharmacophore techniques to identify NAD^+ competitive inhibitors with natural or dietary-derived scaffolds mimicking the adenine or the nicotinamide moieties. In fact, three-dimen-

sional pharmacophore modeling techniques revealed to be useful for virtual screening and computational purposes to analyze diverse compound databases in order to define pharmaceutical values of new compounds [116, 117]. Interestingly, the use of less-sophisticated techniques based on topological-structural descriptors and subsequent statistical treatment, i.e., discriminant analysis, have also been demonstrated as very efficient methodologies for the selection of new natural compounds. Even in this case, the validated model could be readily applied for searching new chemicals of natural origin in large databases [118, 119]. It is expected that the usage and combination of various *in silico* approaches and the availability of compound databases of natural and dietary sources (see below) could constitute an effective step toward the identification, development, and pharmacological definition of natural and dietary-derived components in metabolic and epigenetic mechanism of cancer.

5.4.2 Chemical Space of Natural and Food Compounds

Since natural products and dietary components are known to represent a vast chemical diversity with underlying scaffold complexities and architectures, exploring the chemical space of these compounds it currently a major field of research for different groups [13, 120–125]. Most of the natural products are assorted by chemical groups reflecting novel molecular properties/features as compared to synthetic compounds and available drugs. Several chemoinformatic analyzes, in fact, highlight this behavior and, at the same time, recognize the adherence to drug- and lead-like rules purporting the idea that several classes can be considered as pharmaceutically relevant entities [13, 124]. In addition, despite this diversity, natural products insure the presence of privileged scaffolds that could offer the advantage to address the coverage of poorly explored chemical space [121, 126]. As previously indicated, this feature is particularly appealing for industrial settings to insure the appropriate intellectual property protection requested for the pharmaceutical development. In this direction, it should be noted also that natural products are providing line principles for novel library design in combinatorial chemistry and targeted compound libraries inspired by nature [126–128].

From the chemical point of view, the analysis of natural products databases available in the public domain shows a low-molecular overlap of compounds and highlight as the most representative molecular fragment benzene, acyclic compounds, flavones, coumarins, and flavanones [121, 122, 125]. A particular class of natural compounds that can be considered as dietary component are flavoring substances like menthol, camphor, and anethol, that are discrete chemical entities that usually are considered “generally recognized as safe” (GRAS) compounds. Interestingly, the comparison of collections of compounds including GRAS, natural products, approved drugs, and dataset from commercial molecules by means of chemoinformatic analysis demonstrated that GRAS products are an important source of bioactive compounds that possess all the characteristics for drug discovery and nutraceutical purposes [13].

Among computational approaches that can help driving the discovery of new bioactive compounds, a prominent workflow is the screening of large database of readily available molecules. It is with surprise that the scientific community has not developed yet a freely available and fully chemically annotated database of food components [8, 9]. Despite this lack, some examples are starting to appear in the literature and on the Internet. Among them, we can list the INFOODS of FAO [129], the USDA national nutrient database [130] and the FooDB that has been recently released [131]. In the direction of the creation of a comprehensive and freely available collection of food chemicals, it should be noted also the necessity to include the possible procurement from commercial sources of purified samples of food components that, ideally, should complement the major efforts that have been done in the past years for other natural sources [123].

5.5 Conclusions

Many anticancer drugs have natural origin or are the result of chemical optimizations of natural scaffolds. Because the natural product landscape constitutes a varied supply of building blocks and intermediates, they can represent the starting point for generating lead compounds with bioactive relevance. A thriving topic in cancer research deals with metabolism and epigenetics mechanisms that lead to malignant transformation and the way to interfere pharmacologically with the pathogenesis and progression of cancer diseases by means of small molecules. Natural and food-derived compounds able to modulate epigenetic and metabolic mechanisms are of great interest because they promise to provide new therapeutic interventions, as they are capable to exert anti-inflammatory, antiangiogenic and antioxidant effects that could also be beneficial for anticancer purposes. In this framework, it is expected that advances in computational approaches, with emphasis on pharmacophore and docking-based techniques, together with the systematic cataloguing of natural and dietary-related components, would greatly help to track molecular mechanisms involved in nutriepigenomics and nutrimetabolomics, and therefore constitute a launching platform for new drug-discovery pipelines.

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