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Review

The Role of DNA Intercalators and Acridine Derivatives in Cancer Chemotherapy

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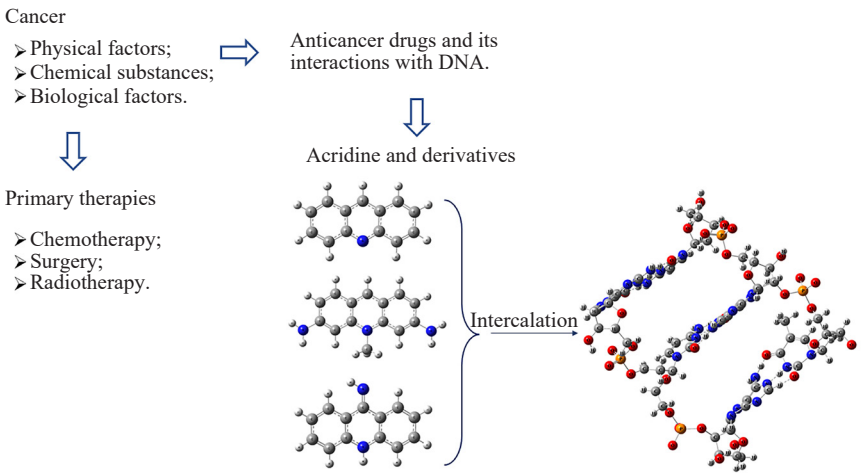

Abstract: Cancer is characterized by the accumulation of Deoxyribonucleic Acid (DNA) damage; consequently, drugs used in cancer therapy target DNA and interact with nucleic acids through covalent bonding, groove binding, electrostatic interactions, and intercalation. Therefore, this review encompasses a bibliographic survey of the historical, structural, and functional aspects of DNA, the main characteristics of carcinogenesis, and how medicines interact with DNA, especially acridine and its derivatives. Among the factors that contribute to cancer are physical, chemical, and biological factors. Most DNA damage caused by these factors can be corrected by repair enzymes; however, when these enzymes fail to fully correct the damage, permanent point mutations may result. Modern approaches to drug discovery have focused their studies on understanding how the interaction with the target site occurs. In this context, intercalation

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is the insertion of planar molecules, intercalators, between the base pairs of the double helix. These compounds are stabilized by π-π interactions and hydrogen bonds, causing conformational changes, hardening of the DNA, and interruption of the cell cycle. Among the classes of intercalators, acridine and its derivatives stand out, which have excellent anticancer properties. Finally, it is hoped that this review will enhance understanding of DNA, drug-DNA interactions, acridine and its main derivatives, and provide a solid foundation for students and researchers who want to study the topic of cancer.

***Keywords*:** carcinogenesis, acridine, acridine derivatives, DNA, epigenetic, intercalators

1. Introduction

Cancer is a complex disease that can arise from different causes, and its spread and progression are influenced by several factors, including hereditary and environmental factors, which lead to the transformation of normal cells into tumor cells, causing disordered growth and consequent invasion into surrounding tissues and spreading to other organs.[1,2] Therefore, cancer is a major global health issue and one of the leading causes of death worldwide. Although traditional treatments offered by healthcare systems—such as chemotherapy, surgery, and radiotherapy—play important roles in managing tumors, the pathological process of cancer remains highly complex.[3,4]

The formation of tumors involves many steps, including mutations in Deoxyribonucleic Acid (DNA), because the DNA molecule is the basic genetic material responsible for the normal activities of life and the stable characteristics of species, and it is essential to maintain its stability.[5,6] When a structural change occurs in DNA, it implies an alteration in a relevant gene; thus, cells begin to divide uncontrollably owing to variations in the DNA structure, resulting in abnormal function and cancer growth.[7,8]

DNA is the cellular target of several antineoplastic agents because most anticancer drugs are small molecules capable of blocking signal transduction pathways for tumor growth and proliferation, acting mainly as DNA-intercalating cytotoxic agents. These intercalating agents or intercalators cause structural changes in DNA by interacting with the base pairs of the nucleic acid, lengthening its chain after the double helix unwinds.[9,10]

Intercalators are mutagenic as they delay or inhibit DNA transcription and replication.[11,12] Intercalating molecules generally have heterocyclic structures and intercalate between DNA base pairs through π–π interactions or hydrogen bonds, causing conformational changes and changes in cellular replication.[13,14] Due to its promising characteristics, there is a growing need to discover new intercalating molecules and to synthesize new anticancer drugs.[15]

An example of an intercalator is acridine, a flat, heterocyclic molecule composed of two aromatic rings fused to a central pyridine ring, in which one of the central CH groups is replaced by a nitrogen atom. During the intercalation process, acridine inserts itself between polynucleotide chains, causing conformational changes in the DNA, impairing its function, and compromising cell division, which can trigger apoptosis.[16,17] The synthetic versatility of acridine, enabled by chemical modifications to its structure, has allowed for the development of derivative compounds with distinct biological activities such as antiparasitic, antibacterial, anti-inflammatory, antioxidant, and antifungal properties[18-21] significantly contributing to the expansion of its pharmacological profile.[15,22]

Given the relevance of this molecule as a structural foundation for the development of new compounds and, consequently, new drugs, investigations into acridine and its derivatives are essential, particularly in highlighting their characteristics, specificities, and interactions with biomolecules such as nucleic acids. According to Żamojć et al.,[23] understanding the various drug–DNA binding modes is crucial for elucidating the pharmacokinetic and pharmacodynamic profiles of these substances, enabling the design of novel intercalating compounds with enhanced therapeutic efficacy.

Therefore, this review aims to compile and discuss the main structural and functional features of acridine and its derivatives, with an emphasis on their mechanisms of interaction with DNA and their potential as antitumor agents. Evaluating these interactions may significantly contribute to advancements in cancer therapy and the discovery of new, effective drugs for cancer treatment.

2. Structure of DNA

Deoxyribonucleic Acid (DNA) is a polymer organized in a double helix, with each strand composed of monomers called nucleotides. These nucleotides are joined together by phosphate groups, which form bonds between the 5' carbon of the deoxyribose in one nucleotide and the 3' hydroxyl group of the deoxyribose in the next, thus creating a polynucleotide chain. The phosphate group attaches to the pentose sugar via ester bonds, resulting in an overall structure held together by phosphodiester bonds. The phosphate group bonded in the pentoses carries a negative charge, which imparts an overall negative charge to the DNA molecule.[24,25]

Each DNA nucleotide (Figure 1) is composed of three molecular fragments: a phosphate group, a five-carbon sugar (deoxyribose) and a heterocyclic base. Phosphate groups and sugars constitute the backbone of each DNA strand, serving a structural role while also being hydrophilic. In the intracellular environment, they remain in contact with the aqueous solution. The nitrogenous bases, which are bonded to the sugar and termed nucleosides, protrude laterally and are hydrophobic.[9,25,26]

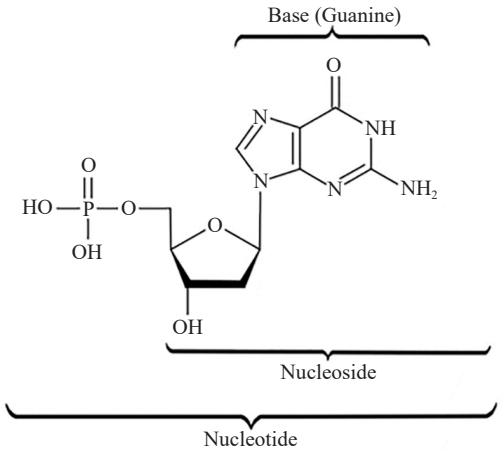


Figure 1. Structural representation of a nucleotide: the base (example: guanine) and the nucleoside

The orientation of DNA has several binding sites, resulting in the formation of two cavities known as the major or main groove and the minor groove.[27] These grooves differ significantly in size, shape, electrostatic potential and position of hydrogen bonding sites.[26,28]

The minor groove is an important molecular target for many DNA-binding molecules of interest because it has a higher density of negative charge compared to the major groove. Additionally, there are fewer functional groups exposed towards the minor groove than in the major groove.[29,30] In contrast, small molecules that bind to the major groove can directly compete with transcription factors and other DNA-binding proteins.[31]

3. Function of DNA

DNA is considered the fundamental molecule of life as it regulates numerous biochemical processes within the cellular system. It acts as the executor of genetic processes, ensuring the replication of genetic information in living organisms, and plays an essential role in protein and enzyme synthesis through the transcription process.[32,33]

Replication is an essential process in all forms of life, aiming to faithfully transmit the genetic information encoded in mitochondrial and nuclear DNA to daughter cells during somatic cell division and to gametes for the inheritance of the "chemistry of life" in the next generation.[34]

This transmission of information and genetic characteristics from one generation to the next through DNA is known as heredity; This concept has been elucidated through studies over the years, initially based on the discoveries

of Gregor Mendel in the 19th century. Mendel's work described the inheritance of characteristics in pea plants, suggesting that specific "factors" (established today as genes) are responsible for the transfer of genetic information and consequently characteristics of the organism between generations, which was later possible to determine as the principles of heredity.[35-37]

The hereditary transmission of characteristics depends on genes, which are maintained as DNA sequences. This transmission refers to characteristics passed from one generation to the next or from one mother cell to two daughter cells. Genes are responsible for the production of proteins. Therefore, the information encoded in a specific gene is transferred to a specific protein. Consequently, a complete set of proteins defines the structural and functional characteristics of a cell. This also includes observable characteristics in parents that can also be seen in descendants. These characteristics range from physical aspects such as eye color, hair type, height and even predisposition to certain diseases.[38-40]

For hereditary transmission to occur, DNA replication must proceed precisely and efficiently. It begins with the unwinding of double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA), facilitated by enzyme DNA helicase and DNA polymerase, responsible for synthesizing the newly replicated strands. These and other replication enzymes (replisomes) coordinate unwinding and synthesis at the replication fork; in the elongation phase, the replisomes travel in opposite directions along replication forks, unwinding the DNA helix and synthesizing complementary daughter DNA strands using the parental tapes as templates. Another important enzyme to be mentioned is topoisomerase, which resolves DNA supercoils that accumulate during replication and ensures the progression of replication forks and the maintenance of genome stability. Once replication is complete, the replisomes are disassembled. This process is known as semi-conservative replication.[41-45]

Following replication, another important function of DNA is transcription, which serves as a bridge for translating genetic information. In all organisms, transcription can be summarized as the initial phase of protein-coding gene expression.[46,47]

In this way, the sequence of bases present in the DNA coding strand will determine the sequence of bases in the Ribonucleic Acid (RNA) molecule and base pairing occurs between the newly formed single-stranded RNA molecule and the DNA bases. Thus, nucleotides are added by RNA polymerase to the 3' end of the growing RNA strand, and RNA synthesis continues in the 5' to 3' direction as does DNA synthesis. It is worth noting that this RNA transcript carries the same information as the coding DNA and acts as messenger RNA (mRNA).[48-50]

Translation is the second step of gene expression. While transcription occurs in the nucleus of the cell, translation takes place in the cytoplasm. The information contained in mRNA is used to drive the synthesis of polypeptides, with the amino acid sequence being determined by the nucleotide sequence of the RNA. In other words, the genetic information carried by mRNAs is "transformed" into functional proteins through translation. Thus, translation requires ribosomes, transfer RNA (tRNA) and a set of enzymes to promote the binding of each amino acid with its corresponding tRNA molecule.[51,52]

To initiate translation, the ribosome, along with tRNA, must be positioned at the initiation codon present in the mRNA. Ribosomes translate one codon at a time, sequentially adding amino acids to the developing polypeptide chain. This entire process occurs via tRNA, which connects the information from the mRNA to the peptide sequence of the protein that is being formed. In this way, it can be considered that tRNAs are the "translators" of genetic information.[53-55]

4. Relationship between DNA and cancer

Cancer is a complex set of pathological conditions that gradually evolve, resulting in a scenario where cells exhibit uncontrolled growth. These cells possess the ability to evade apoptosis, the natural mechanism of cell death, and are resistant to growth-inhibitory signals. Furthermore, they can cause damage to the extracellular matrix and manifest through tissue invasion, as well as dissemination to other parts of the body.[56,57]

Cancer presents different types of genetic mutations in somatic cells for a significant period of time. These mutations can be described as point mutations, deletions, insertions and genetic rearrangements,[58] and occur due to the influence of some genomic, epigenomic and/or cellular physiological factors such as transcription and replication.[59] These mutations arise through DNA damage and failures in repair processes. When DNA damage is on the transcription strand, Ribonucleic Acid (RNA) polymerase progression is halted, which triggers the recruitment of Nucleotide Excision Repair

(NER) complexes to correct the damage. During the replication process, it is extremely important to maintain the integrity of the DNA and preserve the content of genetic information, but even with the DNA repair mechanisms associated with the replication process, some errors can still occur during the polymerization process in the DNA strands.[60-62]

Although most of these errors are corrected by DNA repair enzymes, which detect irregularities in the geometry of base pairs, some may persist, leading to permanent point mutations. These mutations impact the translation and transcription processes, thus affecting some particularities of the genetic material, such as the folding and functions of the proteins encoded by the modified DNA.[63,64]

Genomic insertions are characterized as rearrangements in which one or more donor sequences are inserted at a non-adjacent locus within non-homologous chromosomes or on the same chromosome, and result in incorrect repair of DNA lesions. Mainly highlighted are Double-Strand Breaks (DSBs), which are common features of cancer genomes. In other words, if DSBs are repaired incorrectly, they can cause genome rearrangements, which are consequently the hallmarks of cancer. It is worth noting that rearrangements can account for up to 2% of germline Copy Number Variations (CNVs) and are often associated with developmental abnormalities. However, the exact mechanisms responsible for these rearrangements are still poorly understood.[65-67]

Through studies of chromosomal rearrangements in immune cells, it was consolidated that genome rearrangements occur through the direct connection of two DNA fragments, which supports the hypothesis that the origin of genomic insertions occurs through a "cut and paste" mechanism. This mechanism consists of a free piece of extrachromosomal DNA that is directly ligated into a chromosomal DSB site.[68-70]

Deletions are mutations in DNA that cause the incorrect expression or absence of one or more amino acids, which has a profound impact on the organism. When the deletion occurs in a small number of bases it becomes more challenging to detect when compared to deletions in a large piece of DNA.[71,72] For example, deletion of exon 19 is associated with the development of Non-Small Cell Lung Cancer (NSCLC) and thyroid cancer.[72,73]

Deletions are also widely studied in mitochondrial DNA, because the mitochondrial DNA (mtDNA) genome has the function of encoding genes that produce cellular energy, being a regulator of mitochondrial function and modulating mtDNA release and replication.[74] Thus, mtDNA breakage and aberrant replication cause deletions within mtDNA. In hereditary and acquired diseases, there is the presence of patterns similar to deletion breakpoint sequences.[75]

Some types of cancer are also associated with hereditary predisposition, as many germline mutations occur in tumor suppressor genes. These genes have the function of maintaining the integrity of the genome and play important roles in DNA repair. When deleterious mutations occur in these genes, it increases the chances of developing breast, ovarian, prostate and pancreatic cancer.[76-78]

Furthermore, some environmental and behavioral factors may be associated with an increased risk of developing neoplasms. This relationship is studied through epigenetics, which involves chemical modifications to DNA, Figure 2.

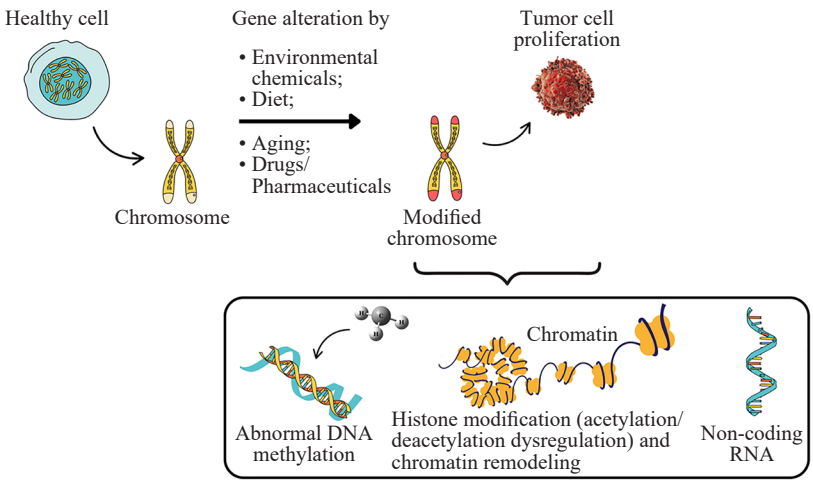


Figure 2. Epigenetics factors and consequences

As examples of epigenetic modifications, DNA methylation, histone modifications, chromatin remodeling and non-coding RNA regulation are factors that contribute to the formation and evolution of cancers. These modifications work in different ways to affect gene expression, and thus critically alter genes involved in cell proliferation, growth, and DNA repair. They can be passed to daughter cells and since embryonic development, DNA methylation occurs dynamically and procedurally to ensure that specific genes are silenced or expressed in a specific environment or at a specific time.[79-82]

DNA methylation is a process that involves the attachment of a methyl group, provided by S-adenosylmethionine, to the carbon atom at position 5 of cytosine within a Cytosine-phosphate-Guanine (CpG) dinucleotide, which results in the generation of 5-methylcytosine (5mC). This process is mediated by modification enzymes called DNA methyltransferases (DNMT1, DNMT 3a and DNMT 3b), which are responsible for maintaining and establishing methylation patterns. DNMT1 targets semi-methylated DNA and transmits methylation information from parental DNA to descendant DNA after the replication process, and DNMT 3a and DNMT 3b regulate the methylation. S-adenosylmethionine is used as a methyl donor to methylate unmethylated cytosine-phosphate-guanine sites.[83-86]

DNA methylation controls important biological processes such as genomic imprinting, X chromosome inactivation, chromatin remodeling, as well as post-translation, transcription and post-transcription. As a result of the methylation process, certain gene regulatory proteins bind to DNA, preventing transcription factors from accessing chromatin and this significantly affects gene expression. When regulatory sequences in genes are changed, transcription factors can no longer recognize them.[87-89]

Cancer can also be characterized by abnormal DNA methylation (hypermethylation or hypomethylation).[90,91] During the process of carcinogenesis, the normal methylation process is altered, and manifests mainly as a large number of repetitive sequences and gene bodies with low methylation and CpG islands, especially in promoter regions of tumor suppressor genes, which have a high rate of methylation. As a consequence of these changes, there is an increase in gene transcription and incorrect production of mRNA. Thus, the frequency of gene translocations, gene mutations and gene breaks increases, and chromatin becomes unstable and loose. Therefore, many factors act together and lead to the occurrence of cancer formation.[92]

The degree of methylation and normal methylation sites, when affected in the genesis of cancer, presents mainly as global hypomethylation of the gene and hypermethylation of individual sites, such as the promoter of tumor suppressor genes, which demonstrate a state of non-methylation or low methylation in normal cells.[79,88] Some mechanisms are explored to understand how DNA methylation triggers cancer pathogenesis. For example; hypomethylation of the TRIM27, LDHA, SEPTIN7 and LIMD2 genes has been associated with breast cancer metastasis, invasion and proliferation.[87]

Studies by Salas et al.[92] indicate that in addition to SEPTIN7, all of these genes present a negative correlation between gene expression and DNA methylation in breast cancer samples. Research by Ambatipudi et al.[93] showed that menopause can accelerate age-related epigenetic pathologies, including cancer, and reported that the accumulation of DNA methylation can increase susceptibility to the development of postmenopausal breast cancer.

Several genes involved in metabolizing drugs and repairing cellular damage caused by themselves or other agents play a crucial role in the development of drug resistance.[87] Epigenetic drugs, particularly DNA Methyltransferase inhibitors (DNMTi), represent a promising class of therapeutic agents in the prevention and treatment of cancer,[94] because they work by reversing irregular epigenetic modifications, which are frequently observed in cancer cells, such as breast cancer, for example. Medications such as decitabine and azacitidine show promise in treating malignant tumors that can demethylate hypermethylated tumor suppressor genes, restoring their normal function.[95]

Histones are proteins that condense DNA into chromatin and are fundamental in the packaging and regulation of DNA, then form the structural core of nucleosomes and play a structural role. Histone modifications occur on their side chains or tails, which critically influence chromatin dynamics and gene expression.[80] Histone modifications (PTMs) are one of the most important epigenetic changes that occur in the post-translational stage. These modifications can regulate diverse genetic processes, such as DNA repair, influencing chromatin structure and transcription, and recruiting remodeling enzymes or transcription complexes.[96] These modifications are related to chromosome remodeling and function and play a primary role in cell growth, cell fate degradation, and carcinogenesis.[97]

Histone PTMs and their levels are balanced by the activities of histone-modifying enzymes, which remove or add histone marks.[98] These modifications include the addition or removal of functional groups and impact the charge density

between histones and DNA, modulating the chromatin architecture and the transcription process.[99] These modifications, such as methylation, acetylation, phosphorylation and ubiquitination, impact gene expression and alter the ability to fold DNA and make some genes unreadable for cells.[100]

Post-translational methylation in histone tails occurs at the arginine (R) and lysine (K) residues of histone H3 and H4. Histone Methyltransferases (HMTs) catalyze the addition of methyl groups to lysine residues.[96] Disordered histone methylation disrupts the balance between the transcription of oncogenes and tumor suppressor genes, contributing to the development of cancer.[101]

Histone acetylation is a reversible and dynamic process characterized by the addition of an acetyl group from acetyl-Coenzyme A (acetyl-CoA) to the amino lysine group at the N-terminus, mainly of histones H3 and H4, regulated by Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs).[102] Acetylation becomes essential for genetic transcription, because when the acetyl group is added, this modification can reduce the electrostatic interaction between histones and DNA, neutralizing the basic charge on unmodified lysine residues, and thus affecting the chromatin state and regulating its structure and intracellular Ph.[103-105]

Histones, which are positively charged, bind tightly to DNA, which is negatively charged. Histone acetylases neutralize the positive charge of histones, which weakens the interaction between DNA and histones, relaxing the structure of the nucleosome and allowing DNA to bind more easily to transcription factors, which is generally associated with activation transcriptional. On the other hand, histones deacetylated by histone deacetylases bind tightly to DNA, densely compacting chromatin and repressing genetic transcription.[104,106] It is worth noting that histone deacetylation is modulated by DNA methylation through the binding of repressor proteins to methylated DNA CpGs. Consequently, Post-Translational Modifications (PTMs) of histones, through deacetylation and acetylation, are fundamental in the regulation of transcription, impacting gene expression.[107]

The dysregulation of histone acetylation is regularly related to the development of cancer, by promoting the aggressive phenotype of cancer cells and consequently the rapid progression of the disease.[108,109] Research indicates that deacetylases (HDACs) are involved in several biological processes, such as cell cycle, DNA replication, differentiation, proliferation, cell death and mitosis. Conversely, when HDCA is inhibited, it can lead to the induction of cancer cell differentiation.[108] For example, histone modification exhibits variations in patterns between breast cancer subtypes, therefore irregular histone acetylation is a driver of expression of tumor suppressor genes and oncogenes.[80,110]

Phosphorylation is another histone modification process, characterized mainly by the phosphorylation of specific amino acid residues regulated by protein kinases and phosphatases that add phosphate groups, at different stages of the cell cycle and physiological conditions. This modification results in the conformational and structural change of proteins, causing cancer target proteins to be inactivated or activated.[111,112]

Ubiquitination is one of the main post-translational modifications in proteins, as it encompasses the covalent attachment of one or more Ubiquitin (Ub) molecules on lysine residues to the target protein, that is, ubiquitin modifies target proteins, mainly ligases, through activating enzymes and binding enzymes.[113,114] This modification involves the action of several specific enzymes sequentially, such as E1 activating enzyme, E2 conjugating enzyme and E3 ligase. Ubiquitin is a protein composed of 76 amino acids that contains seven lysine residues and that can undergo further ubiquitination, resulting in the formation of mono-, multi- or poly-ubiquitin chains that are interpreted in different ways by the cellular machinery.[115-117]

Ubiquitination of histones such as H2A and H2B is an important post-translational modification in the DNA damage response, as it forms an essential part of the regulatory network that directs the DNA damage response.[117,118] At different sites, ubiquitination on histone H2A leads to different physiological consequences, since during the response to DNA damage, ubiquitination of H2A by the BRCA1/BARD1 proteins can promote Homologous Recombination (HR), while ubiquitination by the RNF168 protein seems to favor non-homologous splicing repair.[117,119] H2B ubiquitination is essential for the functionality of the tumor suppressor protein p53.[120]

The integrity of DNA is constantly threatened by exposure to exogenous and endogenous chemicals, Ionizing Radiation (IR), Ultraviolet (UV) radiation and errors in DNA replication, which compromise and damage the genome. In order to mitigate this problem, cells have effective mechanisms, known as DNA damage responses, which in addition to detecting and signaling, also repair DNA damage. These processes are fundamental to the physiology of cells, and their deregulation or failures can cause genomic instability syndromes associated with cancer, developmental defects, infertility, stem cell exhaustion, immunodeficiency, premature aging and neurodegenerative diseases.[118,121]

Another epigenetic modification worth highlighting is chromatin remodeling. Chromatin is characterized by a mixture of DNA and proteins that make up the chromosome. In its condensed form, also known as heterochromatin, the chromatin fibers coil in a compact and firm way, accommodating themselves densely within the cell nucleus. This arrangement inhibits gene transcription, requiring chromatin remodeling so that it transitions to a state more relaxed, known as euchromatin, thus allowing gene expression.[80,122]

To facilitate the binding of transcription factors, condensed chromatin undergoes a transcriptionally accessible state, and may entail various changes in the position of the nucleosome, such as changes in the spacing between DNA regions or changes in their relative locations. Chromatin remodeling also includes the removal of histones or their replacement with variants that are associated with active transcription.[80,123] Even facilitating cellular function and transcriptional regulation, chromatin remodeling plays a crucial role in the pathogenesis of diseases, especially cancer.[81,124]

Changes in chromatin structure impact various biological functions such as telomere protection, differentiation, replication, transcription, genome stability, and DNA damage repair.[125] Histone modification also affects the state of chromatin, as deacetylases (HDACs) convert euchromatin to heterochromatin by removing acetyl groups from histone tails, leading to the silencing of chromatin and tumor suppressor genes.[104] For example, acetylation may be associated with the opening or activation of chromatin, while deacetylation of lysine residues leads to compression of chromatin, inactivating genetic transcription.[126]

Non-coding RNAs (ncRNAs) are RNA molecules that, although not translated into proteins, perform several biological functions and gain prominence as key regulators in cellular processes. According to the size of ncRNAs, they can be divided into two subclasses: NcRNAs smaller than 200 nt nucleotides are called small or short non-coding RNAs, while those larger than 200nt are called long non-coding RNAs (lncRNAs) and both groups are quite heterogeneous.[127,128]

The ncRNAs are recognized for their ability to recruit and direct protein complexes that modify chromatin to specific genomic loci, this action causes significant changes in histone modifications, DNA methylation and the general structure of chromatin.[80] The lncRNAs are transcribed by RNA polymerase II and undergo splicing, polyadenylation and capping, as in messenger RNAs (mRNA), can recruit enzyme complexes and chromatin modification or remodeling complexes to specific locations, and thus alter the structure of the chromosome, the DNA/RNA methylation status and then repress or increase the transcription of target genes.[128-130]

In general, lncRNAs can influence the expression of one or several genes, because regulate the expression of many protein-coding genes by direct or indirect processes, and have diverse functions, such as transcriptional management, chromatin alteration, translation regulation, modulation of protein activity and organization of the nuclear domain. Many oncogenic lncRNAs contribute to the development of cancer, mainly by inhibiting the expression of tumor suppressor genes and cell apoptosis, or by promoting increased cell proliferation and metastasis. As described in in vivo and in vitro studies and tests, regulatory ncRNAs associated with cancer development have been identified as oncogenes or tumor suppressors.[130-133]

In breast cancer, for example, ncRNAs are often found overexpressed or mutated, as these changes deregulate or disrupt normal epigenetic mechanisms, which contributes to cancer epigenetics. Several ncRNAs in breast cancer, for example, have been associated with the modulation of crucial epigenetic factors, such as DNA Methyltransferases (DNMTs) and Histone Deacetylases (HDACs). These interactions significantly impact the methylation and acetylation status of DNA and histones, influencing essential cellular processes such as differentiation, proliferation, invasion, and metastasis.[80,126]

Unlike genetic mutations, epigenetic changes do not alter the DNA sequence, but affect how genes are expressed, for example, the same epigenetic modification can have different functions in different types of cells or under varying environmental conditions, this is due to the fact of the dynamic nature of specific epigenetic changes as causal factors in the development of diseases.[80]

In general, epigenetic changes such as histone deacetylation and DNA hypomethylation are influenced by pharmacological interventions, called epidrugs. These epigenetic medicines are chemical compounds that alter the structure of DNA and chromatin, promoting the reversal of transcriptional and post-transcriptional changes. They act mainly by regulating the enzymes responsible for these modifications, reactivating tumor suppressor genes and DNA repair genes that have been silenced by epigenetic mechanisms. And when combined with standard chemotherapy, epidrugs have treatment success rates.[134,135]

These drugs that target epigenetic modifications point to a promising direction in cancer therapies, utilizing DNA Methyltransferases (DNMT), histone-modifying enzymes, and mRNA regulators to combat changes. For example, the drugs decitabine and Azacitidine (AZA), DNMT inhibitors, are already approved by the Food and Drug Administration (FDA) and are used for myelodysplastic syndromes and AZA for acute myeloid leukemia and chronic myelomonocytic leukemia.[136]

As mentioned previously, physical factors can cause carcinogenesis and occur through non-ionizing electromagnetic radiation that causes direct damage to DNA; ionizing radiation (more than 10 eV as Ultraviolet (UV) radiation (10–125nm), X-rays, gamma radiation, alpha radiation) that generates Reactive Oxygen Species (ROS) as alkoxy ($RO_2^{\bullet}$) and hydroxyl superoxide ($O_2^{\bullet}$), hydroxyl ($HO^{\bullet}$), and singlet oxygen ($^1O_2$) or by repetitive trauma.[137,138]

Chemical carcinogenesis is the most diverse group and has numerous carcinogenic substances such as Polycyclic Aromatic Hydrocarbons (PAHs), aromatic amines, nitro compounds, alkylating agents, dyes, Volatile Organic Compounds (VOCs), Particulate Matter (PM), asbestos, chlorine, arsenic, Trihalomethanes (THMs), Lead, Cadmium, Mercury and other substances. Given the numerous carcinogenic substances, environmental factors pose serious risks to human and animal health as contamination of soil, water and air is directly related to cancer.[138,139]

In addition to physical and chemical factors, biological carcinogen can occur by parasites, bacteria, fungi, or viruses. As described by Wadgaonkar,[137] the biological mechanisms that cause carcinogenesis are: 1) persistent inflammation that causes DNA damage and mutagenesis; 2) initiation of oncogene expression or inhibition of tumor suppressor activity; 3) evading the immune action of the host.

The physical, chemical or biological factors can cause damage or lesions to DNA, which is a crucial step in the carcinogenesis process. Surgery, chemotherapy, and radiotherapy are the primary therapies used clinically to treat cancer and, although widely used, they present some problems such as side effects, toxicity, drug resistance and recurrence.[139,140]

Some alternatives seek better efficiency in a safer way for the patient. Some alternatives that can be highlighted are Phototherapy including the photothermal and photodynamic therapy.[139] Targeted drug conjugates that are developed with conjugating cytotoxic agents with highly specific targeting molecules, enhancing the specificity of cancer treatment and achieving lower systemic toxicity than traditional chemotherapy such as antibody-drug conjugates is a new modality in cancer therapy.[141] Finally, the use and discovery of specific substances can also contribute to the success of cancer treatment, and the study of interactions between DNA and molecules with therapeutic potential can provide an advance both in the treatment of cancer and other genetic diseases.[142]

5. Intercalation and interactions with DNA

Anticancer drugs can bind to DNA through covalent and noncovalent interactions as described in Figure 3.

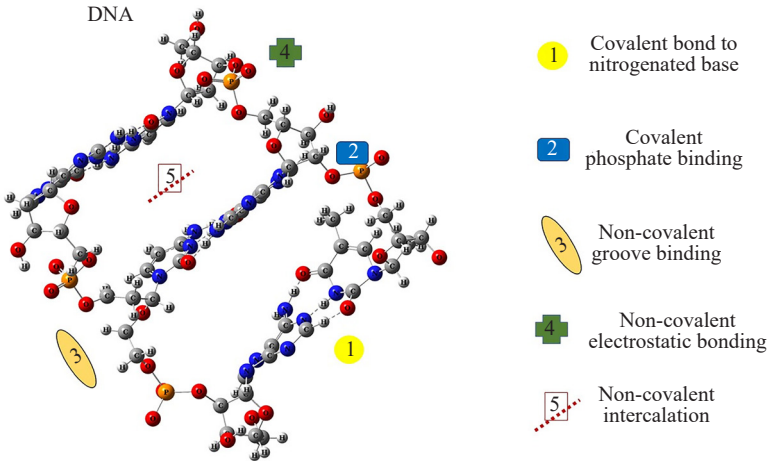


Figure 3. Representative scheme of potential modes of interaction of molecules with DNA

The covalent bond chemically modifies the constituents of DNA and is irreversible, causing complete inhibition of nucleic acid processes and consequently cell death. It is typically formed between metallic ions and the donor atoms of the DNA molecule.[143] In Figure 3, the possibilities for forming covalent bonds are represented in detail. In item 1) it is possible to observe the formation of covalent bonds at the junction of the bases with the drugs; in item 2) the bond occurs in phosphorus. It is important to highlight that bonds are more energetic than molecular interactions, which increases the formation of DNA adducts. This can result in substantial cytotoxicity because the DNA damage is not easily repaired and can lead to cell death. It is important to highlight that all substances must be evaluated, then the drug can be highly toxic, potentially leading to side effects due to damage to normal cells.[143,144]

Non-covalent interaction occurs through groove binding, electrostatic binding with the sugar-phosphate structure and intercalation, which causes changes in the DNA conformation, Figure 3 item 3), 4) and 5). Additionally, these interactions can disrupt DNA-protein interactions and lead to breaks in the nucleic acid chain.[144,145] The drug-DNA complex formed by noncovalent binding can be more easily disrupted, leading to a reduced duration of action. Consequently, these drugs might require more frequent dosing or higher doses to achieve therapeutic effects.[143,145]

Groove ligands interact with the major groove and minor groove of DNA, through covalent bonds, cross-links, or through weak interactions. However, most molecules bind to the minor groove of DNA because the major groove interacts with transcription factors and other DNA-binding proteins. Therefore, groove ligands disrupt the interactions necessary for most bonds of transcription factors.[146-149] Electrostatic binding occurs when positively charged drug molecules interact electrostatically with phosphate groups in DNA, which are negatively charged, Figure 3 item 4).[150]

Modern approaches to drug discovery have focused their studies on understanding how the interaction with the target site occurs. Some substances may compete between intercalation and their binding to the groover or just bind to the groover.[151-153] DNA groove binders represent a promising niche of study and some examples of anticancer substances that bind to the DNA groover are: Flavonoids such as troxerutin that binds to DNA at a minor groove and exhibits cytotoxicity in cancer cells;[151] and other substances of commonly studied as: Brostallicin, Distamycin, Ridinilazole, Tallimustine and others.[152]

Different from other types of interaction/bond, intercalation is defined as a process of insertion of molecules with specific chemical properties between adjacent base pairs of the double helix, Figure 3 item 5). This insertion is stabilized by π–π stacking between base pairs, Van der Waals forces, hydrogen bonds, hydrophobic charge transfer, and electrostatic interaction, resulting in the unwinding, elongation and hardening of the DNA, causing cell cycle arrest and cell death. These small ligand molecules act as drugs when they cause some alteration or inhibition of DNA functions, which makes them necessary to cure or control a disease.[10,154-156]

As a result of intercalation, the DNA skeleton is modified, losing its regular helical structure. Consequently, the torsion angles involving the sugar-phosphate groups are altered in order to accommodate the compound, resulting in the separation of base pairs at the site of intercalation. This process causes elongation and unwinding of the double helix, resulting in an increase in the distance between the phosphates.[9,157,158]

Some large groups of compounds that are interspersed between DNA base pairs are classified as follows: anthracyclines, anthracenes, phenanthridines, phenanthrolines and acridines, all of which have other related compounds and derivatives. Anthracyclines intercalate between DNA base pairs, inhibiting topoisomerase-II and DNA and RNA synthesis. The quinone present in the molecular structure of anthracyclines is responsible for generating reactive oxygen species and consequently their cytotoxicity, in addition to blocking specific transcription factors.[159-161] Among the anthracyclines in clinical use, the first-generation drugs are daunorubicin and doxorubicin, which play an important role in the treatment of human lymphomas, leukemias and breast carcinomas.[157,160]

However, both daunorubicin and doxorubicin have cardiotoxic effects, which can cause heart failure, low target specificity and acute toxicity to healthy cells, as well as nausea, vomiting and hemorrhage. However, the side effects of these medications can be reduced by ensuring targeted administration of the medication to the cancerous region.[162-164]

The study by Munir et al.[164] theoretically evaluated the graphene molecule as a nanocarrier for delivering the anticancer drug daunorubicin using the computational method of Density Functional Theory (DFT). It highlighted the presence of Van der Waals interactions between graphene and daunorubicin, suggesting that the drug could be easily delivered to the target location due to the weak forces between the drug and the nanocarrier. Overall, the calculations developed by the authors proposed that graphene can act as an efficient carrier for the targeted delivery of the drug daunorubicin to treat cancerous diseases.

In more fundamental terms, Density Functional Theory (DFT) represents an approach to the electronic structure of systems. It aims to solve systems in terms of electron density, which is essential for understanding not only chemistry but also a part significance of biology and physics.[165] DFT is essential for offering a perspective on the electronic structure, geometry, energy and chemical properties of systems at the atomic level. This facilitates the understanding of the stability and strengths of interactions between molecules, and identifies the selectivity of molecular systems and chemical reactivity, in addition to allowing the precise characterization of complexes involving transition metals with biomolecules.[166-170]

For example, Tolbatov et al.[170] evaluated the structure, electronic properties and stability of complexes formed by DNA/RNA nucleobases with a metallic fragment generated by auranofin using DFT approaches. They found that the complex formed with this fragment altered the electronic structure of the nucleobases, slightly modifying their complementarity. The authors also demonstrated that computational research generates results that serve as a crucial element for future experimental and theoretical studies.

Anthracene is a simple aromatic compound that consists of three fused benzene rings and exhibits intercalating activity due to its planar geometry, with the ability to form hydrophobic and π-stacking interactions.[171,172] Furthermore, studies by Sun et al.[173] demonstrated that anthracene also binds to the DNA molecule via the groove binding. Bisantrene, a derivative of anthracene, has lower cardiotoxicity than commonly used anthracyclines. Thus, the antineoplastic activity of this compound is attributed to the inhibition of DNA relaxation and supercoiling mediated by topoisomerase II, which prevents DNA replication and consequently the proliferation of cancer cells.[174,175]

Phenanthridines are angularly fused heterocyclic compounds and some naturally occurring alkaloids have the phenanthridine skeleton in their composition, which allows these compounds to exhibit broad biological activities such as antibacterial, antitumor and antileukemic effects.[176,177] Ethidium bromide is a derivative of phenanthridine and when it is intercalated between DNA, it causes stretching and unwinding of the double helix. Additionally, it induces an inclination between base pairs, affecting the twisting and bending flexibility of DNA, as well as biological processes such as transcription and replication.[178-180]

Phenanthroline is a bidentate, rigid, planar and hydrophobic ligand, meaning it can bind to metal ions in two different locations, making it effective in treating cancer when used in combination with other antitumor drugs.[181] In other words, phenanthroline assumes the role of receptor for metal ions, forming a ligand-metal complex.[182,183]

Thus, the intercalation between DNA base pairs by any metal complex requires a flat ligand, such as phenanthroline (phen group) with a metal (platinum (Pt)), forming a complex that distorts the DNA helix through the formation of intra- and interchain cross-links.[184,185] For example, Niroomand et al.[186] evaluated the DNA-binding capacity of the lanthanum complex (III) – phenanthroline, using DFT, and concluded through calculations that the ligand (phen) of the complex has excellent planarity, and therefore interacts easily with DNA. They also suggested that the Lathanum (III) complex binds to DNA through groove binding.

6. Acridine and derivatives

Acridine is an organic dye discovered in 1870 by Carl Graebe and Henrich Caro, who, during an extraction with coal tar, managed to obtain a specific fraction that caught their attention because it caused irritation to the eyes and throat. The compound was later isolated as a pure crystal and given the name Acridine, which derives from the Latin word “acris” and means pungent or caustic.[187-189]

Acridine ($C_{13}H_9N$) is a heterocyclic molecule, formed by two rings fused to a pyridine ring in a central position, also known as dibenzo-pyridine, 10-azaanthracene and 2,3-dibenzoquinoline. It is structurally related to anthracene, but one of the central –CH– groups is replaced by –N– (Figure 4). It has a planar structure that allows it to reversibly bind to DNA and RNA (ribonucleic acid) via intercalation and can normally be found in natural molecules.[158,190-192]

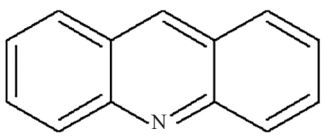


Figure 4. Structural representation of the acridine molecule

The first study on the intercalation behavior of acridines was published in 1961,[193] and since then, this intercalator has been widely used in the development of antineoplastic agents that act on DNA.[194] This characteristic is attributed to the acridine skeleton, as the three fused aromatic rings are large enough to intercalate between DNA base pairs.[195,196]

Thus, the biological activities of acridine are attributed to the planarity of its aromatic structure and the cytotoxicity of acridine-based drugs is based on their ability to suppress topoisomerase activity and consequently interfere with cellular functions.[196,197] The acridine was initially used against bacterial infections, malaria, wound antiseptic and other protozoal infections, and its pharmacological properties were studied for the first time during the First World War.[198,199]

For acridine to be used as an anticancer compound, it must meet certain prerequisites, such as the ability to act as an electron donor or acceptor via its nitrogen atoms and to promote intercalation between DNA bases.[22,200] In this context, the interaction between acridine and DNA may also occur through electrostatic forces.[201] Notably, the nitrogen atom in the acridine structure is the most reactive site of the molecule, making it particularly susceptible to nucleophilic reactions.[202]

One approach to evaluating these properties of acridine is through the analysis of its Frontier Molecular Orbitals (FMOs) (Figure 5). The Highest Occupied Molecular Orbital (HOMO) represents the highest-energy occupied orbital, associated with the molecule's electron-donating ability, whereas the Lowest Unoccupied Molecular Orbital (LUMO) corresponds to the lowest-energy unoccupied orbital, related to its ability to accept electrons.[203-205]

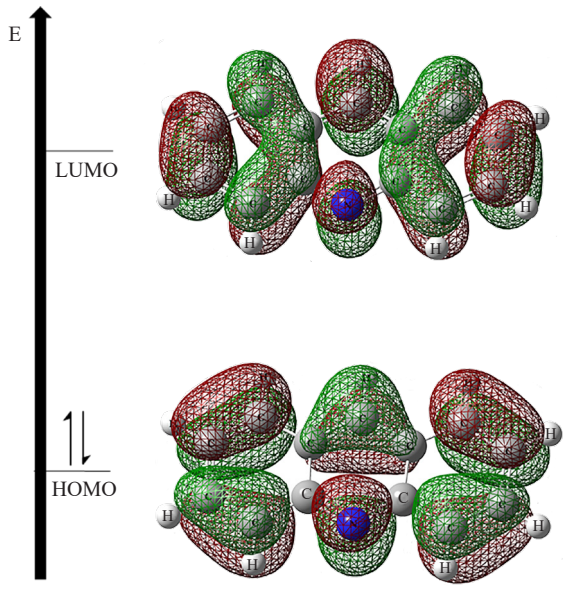


Figure 5. Frontier molecular orbitals HOMO–LUMO for acridine. Data obtained at B3LYP/6-31 + G (d, p) level

Thus, Figure 5 shows that the HOMO and LUMO orbitals exhibit well-defined π orbitals distributed across the aromatic rings of acridine, with the electron density localized over the molecule. This electronic distribution suggests that acridine has the potential to form stable interactions with biological targets, such as DNA, particularly in base pair regions, supporting its function as an intercalator in therapeutic processes and reinforcing its potential as an antitumor agent.

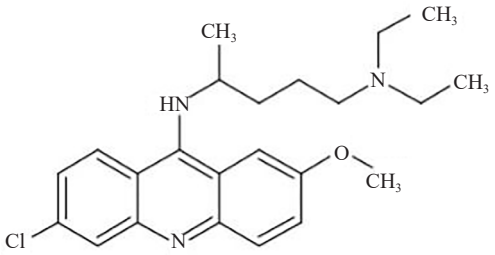
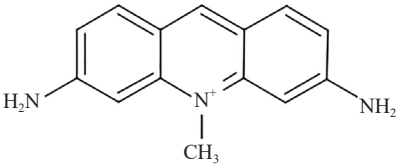
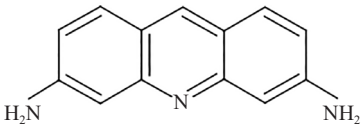
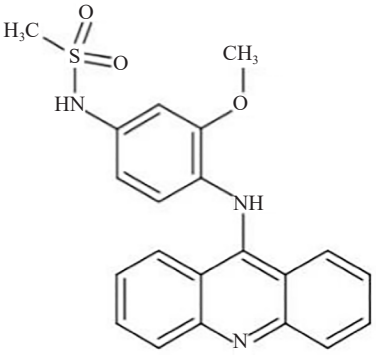
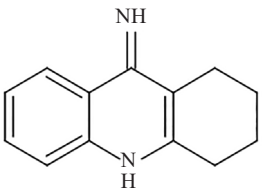
This behavior has been observed through fluorometric and electrophoretic techniques. According to Rao et al.,[20] acridine demonstrated effective intercalation with DNA, showing a strong affinity for adenine–thymine-rich regions. Furthermore, their studies indicate that acridine exhibits significant cytotoxicity against the development of human tumor cells.

According to Vilková et al.,[192] acridine also possesses structural characteristics that enable interactions with topoisomerase I/II and telomerase, playing a crucial role in the treatment of various diseases. Additionally, its structure is considered a privileged scaffold for the development of therapies targeting neurodegenerative disorders.[206]

Despite presenting several therapeutic activities, the main mechanism of action of acridine is its intercalation into DNA. In order to improve the biological and physicochemical properties of acridine, compounds derived from this molecule are studied and produced through structural modification of the aromatic ring, or with the addition of a new chemical group. The aim is to enhance the effectiveness of medicines based on the acridine skeleton. These derived molecules have been used for commercial purposes for many years, precisely because they are capable of interacting with nuclear DNA in a specific way with biological targets.[196,197,207]

Acridine exhibits broad biological activities, leading to the development of various derived compounds. Table 1 shows the most common.

Table 1. Representative structures of acridine derivatives and their respective chemical structures[198,208]

Derived compounds	Functions	Chemical structure
Quinacrine	First clinically studied antimalarial drug	
Acriflavine	First potent antibacterial agent	
Proflavine	Changes DNA structure; interferes with enzymes; antiseptic	
Amsacrine	First drug that works well against topoisomerase II; used in the clinical treatment of leucemia	
Tacrine	Inhibitor of topoisomerases I and II	

Quinacrine, an acridine derivative, is associated with antimalarial activity, as it inhibits the parasite's topoisomerases II. It was the first synthetic antimalarial drug clinically tested and widely used during World War II, but was soon replaced by chloroquine.[208,209]

Recently, quinacrine has been repositioned as a potential therapeutic agent for cancer treatment after being identified in a screening of small molecules that activate the tumor suppressor protein p53. Following this discovery, several studies have been conducted to investigate its antitumor activity in different types of neoplasms.[210-212]

Quinacrine exhibits cytotoxicity against cancer cells through multiple mechanisms, making it a promising candidate as an anticancer agent. Among its main mechanisms of action are DNA intercalation, modulation of nuclear proteins, and interference in multidrug resistance pathways. Additionally, quinacrine induces the activation of p53, a crucial tumor suppressor protein involved in apoptosis and cell cycle arrest in response to genetic damage. At the same time, it inhibits Nuclear Factor kappa B (NFκB) signaling, a key regulator of inflammation and cell survival often overactivated in various types of cancer, whose inhibition contributes to reduced tumor proliferation and resistance.[213,214]

The DNA binding mode of quinacrine is similar to that of other drugs derived from the acridine structure, namely, intercalation. Its planar conformation facilitates stacking between nitrogenous bases, enabling its insertion between DNA base pairs. However, quinacrine's interaction with genetic material is not limited to intercalation. Its diaminobutyl side chain also enables binding to the minor groove of the DNA double helix, providing greater stability to the interaction. Nonetheless, DNA intercalation remains the primary anticancer mechanism of quinacrine.[215]

The cytotoxic effects and mechanism of action of quinacrine were analyzed in K562 chronic myeloid leukemia cells, where it was found to induce apoptosis, increase the production of Reactive Oxygen Species (ROS), cause mitochondrial membrane depolarization, and downregulate the anti-apoptotic genes BCL2 and BCL2L1.[216,217]

Its effects have also been investigated in ovarian cancer cells. According to Thirusangu et al.,[218] quinacrine significantly increased the expression of the proteolytic enzyme Cathepsin L (CTSL) without altering the levels of Cathepsins B (CTSB) and D (CTSD). These results indicate a specific role for CTSL in the induction and promotion of autophagic flux mediated by quinacrine in ovarian cancer cells.

According to Sarkar,[219] quinacrine has shown promise in the treatment of Non-Small Cell Lung Cancer (NSCLC), which accounts for approximately 80% of all lung cancer cases. His study demonstrated that quinacrine exerts significant cytotoxic effects on human lung cancer cell lines A549 and NCI-H520 by promoting the generation of Reactive Oxygen Species (ROS), inducing Endoplasmic Reticulum (ER) stress, and triggering mitochondrial apoptosis. It also revealed interactions between quinacrine and the enzyme GSTA1, inhibiting its catalytic activity. Furthermore, the molecule was shown to modulate apoptotic signaling cascades, suggesting its potential for therapeutic use either alone or in combination with other chemotherapeutic agents for a more effective and less toxic approach to NSCLC treatment.

Quinacrine has the ability to sensitize cancer cells to chemotherapeutic agents and to reverse drug resistance by binding to and inhibiting key proteins involved in multidrug resistance.[220] For instance, in a study by Islam et al.,[221] the use of quinacrine as an adjuvant to reduce the cisplatin dosage in cancer treatment led to increased cell apoptosis, inhibition of colony formation in a colorectal cancer cell line, and suppression of cell proliferation. The study also observed increased sensitivity of cancer cells to cisplatin, overcoming chemoresistance.

Recent studies have also explored quinacrine as a potential inhibitor of SARS-CoV-2 replication. Although SARS-CoV-2 is a single-stranded RNA virus encapsulated by a nucleocapsid, quinacrine may intercalate with viral RNA, interfering with RNA transcription and viral protein synthesis, without affecting host cell Internal Ribosome Entry Site (IRES) functions.[222,223]

Moreover, after viral entry via the endosomal pathway, quinacrine is capable of increasing the pH of endosomes and lysosomes. This pH shift inhibits the activity of lysosomal proteases and prevents the fusion of autophagosomes with lysosomes, hindering viral material release and thereby blocking crucial steps of the viral replication cycle.[223] Quinacrine has also demonstrated in vitro antiviral activity against the Zika virus, Dengue Virus (DENV2), and Ebola virus.[224,225]

Acriflavine (also known as trypaflavin) is an acridine dye, which was first synthesized in 1912, initially used as one of the first antibiotics. However, its use was replaced with the discovery of penicillin. Its biological activity is attributed to its effective intercalation with DNA, acting as a multidirectional drug. It acts as an inhibitor of protein kinases, topoisomerases I and II, in addition to sensitizing drug-resistant cancer cells.[226-228]

Acriflavine interacts with DNA primarily through intercalation between nitrogenous bases and by binding to Topoisomerase I and II enzymes (TOP I/II), forming stable DNA-drug-topoisomerase complexes. This interaction prevents the religation of DNA strand breaks caused by topoisomerases, resulting in extensive regions of cleaved DNA, which triggers the activation of apoptotic pathways. Compounds that act in this way are classified as topoisomerase poisons. Additionally, acriflavine directly affects hypoxia-inducible factors HIF-1α and HIF-2α, which are essential for the cellular response to low oxygen levels. These factors are composed of subunits, and by interacting with them, acriflavine prevents their dimerization, blocking the transcription of target genes related to glucose metabolism and angiogenesis. As a consequence, tumor growth is suppressed, and blood vessel formation is inhibited.[229,230]

The studies by Mangraviti et al.[231] demonstrated that acriflavine is a potent inhibitor of HIF-1α transcription factor dimerization and exhibits significant antitumor activity in the treatment of malignant gliomas. In vitro assays revealed that acriflavine significantly reduced the viability of various brain cancer cell lines, including tumor stem cells, inducing apoptosis in a dose-dependent manner. Furthermore, acriflavine negatively modulated the expression of HIF-1α target genes such as Vascular Endothelial Growth Factor (VEGF) and Phosphoglycerate Kinase 1 (PGK-1), both under hypoxic conditions and, partially, in normoxia. In vivo models showed that local administration of acriflavine via biodegradable wafers implanted intracranially produced remarkable results, leading to nearly 100% long-term survival.

Acriflavine has also been subjected to various in vitro assays to investigate its effects on melanoma metabolism and progression. Research by Martí-Díaz et al.[232] showed that the compound was able to inhibit cell growth in melanoma cells cultured under physiological fasting glucose concentrations in human blood. The inhibition of cell growth was accompanied by an increase in melanoma cell apoptosis and evident DNA damage. The authors also observed that acriflavine intensifies cellular energy stress, promoting selective death of tumor cells under glucose deprivation conditions without significantly affecting normal cells, and induces apoptosis in melanoma cells under normoxic conditions.

The antitumor activity of acriflavine against pancreatic adenocarcinoma was also reported. In vitro models showed that acriflavine blocked epithelial-to-mesenchymal transition and reduced the invasion of human Pancreatic cancer cells (Panc-1), in addition to modulating the immune response by promoting macrophage polarization towards the antitumoral phenotype.[233]

Acriflavine sensitizes bladder cancer cells when combined with cisplatin, as its activity was attributed to the negative regulation of the expression of TOP1 and TOP2A genes, which encode topoisomerase I and II enzymes, respectively. This suggests that the compound may act as an adjuvant agent, enhancing the efficacy of cisplatin in combination therapeutic regimens.[234]

Currently, acriflavine has been shown to be effective against several types of cancer, such as breast, lung, liver, ovarian, pancreatic and leukemia cancer.[228] Furthermore, it has been studied and suggested as a potential medicine for SARS-CoV-2, as it exhibits activity against the enzymes involved in the replication of the coronavirus.[235]

Proflavine (3,6-diaminoacridine) is another planar aromatic molecule, characterized by a polycyclic system with three rings and two flexibles substituent groups,[236] derived from acridine, that has the ability to accumulate in cell nuclei and intercalate between base pairs of double-stranded DNA, altering its structure. This can lead to loosening or fragmentation of the DNA chain and cause mutations in bacteria and viruses due to its toxicity.[237] According to Gatasheh et al.,[237] proflavine interferes with the function of enzymes and also acts as a wound disinfectant (antiseptic).

Proflavine is recognized for its mutagenic effect, acting through intercalation between the base pairs of nucleic acids. This type of interaction confers a specific mutational mechanism, characterized by the induction of insertions or deletions of base pairs, rather than substitutions. It can enter cells and interact with proteins/enzymes and DNA, promoting physiological dysfunctions that culminate in cell death. Additionally, it interacts more effectively with alternating purine-pyrimidine sequences of DNA. Upon exposure to light, it can generate breaks in the double-stranded DNA.[237,238]

In addition to its primary mechanism of action through DNA intercalation, proflavine, due to the presence of charge in its structure, is capable of establishing electrostatic interactions and other non-covalent interactions with a variety of polymers, nanostructures, and ions. During intercalation, the planar ring system of the molecule inserts between the DNA base pairs, while the cationic center, together with the amino groups, promotes specific electrostatic interactions with the phosphate groups of the nucleotide chain, enhancing its affinity for the genetic material's structure.[239,240]

The identification of proflavine's toxic and mutagenic properties led to the suspension of its clinical use for a long period.[239] Due to its intercalating property, it also affects human DNA after exposure, but it possesses abundant

antimicrobial properties, being conventionally used as an excellent antimicrobial agent, as it has the ability to denature bacterial DNA, leading to bacterial lysis.[237]

Another important acridine derivative is Amsacrine (m-AMSA), recognized as the first drug to demonstrate efficacy as a topoisomerase II poison, acting directly in stabilizing the DNA-topoisomerase II complex and preventing the religation of DNA strand breaks. Studies have shown that Amsacrine effectively interacts with both the minor and major grooves of the DNA double helix (ds-DNA), in addition to functioning as an intercalating agent, reinforcing its potential in therapies aimed at inducing apoptosis through genetic damage.[241]

Amsacrine has also been used in the treatment of hematological neoplasms, such as Acute Lymphoblastic Leukemia (ALL). In a study by Escherich et al.,[242] the authors combined Amsacrine with Etoposide and methylprednisolone (AEP) as an intensified therapy for pediatric patients with high-risk ALL. The results showed that the AEP regimen was well tolerated, with no treatment-related deaths or excess infectious complications, and it indicated a trend toward improved event-free survival, meaning without relapses or disease progression.

The efficacy of amsacrine in the treatment of Chronic Myeloid Leukemia (CML) is still under investigation. However, the results from Lee et al.[243] using K562 cells, suggest that amsacrine induces apoptosis, mitochondrial depolarization, and inhibition of the BCL2L1 gene expression. These findings highlighted that this drug works not only through DNA damage but also by suppressing cell survival signaling pathways and exhibiting cytotoxicity in MEG-01 and KU812 cells with CML.

Tacrine was the first acridine-based medicine for Alzheimer's disease, but it was considered toxic to the liver. However, studies have shown that Tacrine works as an inhibitor of topoisomerases I and II, making it possible to interrupt DNA replication and thus reducing the activity of topoisomerase enzymes, which makes it a potential anticancer drug.[198,244] Since the synthesis of tacrine, several derivatives based on its structure have been investigated for their effects on tumor cell lines.[245]

Thus, Wu et al.[246] synthesized the tacrine derivative ZLWT-37, which exhibited significant antitumor effects both in vitro and in vivo, demonstrating its considerable potential as an anticancer therapeutic agent against the colorectal cancer cell line HCT116.

In this context, Solárová et al.[247] investigated the effects of tacrine-coumarin hybrids in various human cell lines, such as human breast adenocarcinoma MCF-7, human lung carcinoma A549, Human Colorectal carcinoma HCT116 (HCT), and murine mammary carcinoma 4T1, aiming to evaluate their antitumor potential. The synthesized compounds demonstrated the ability to reduce cell viability, induce apoptosis, and promote the accumulation of cells in the sub-G0/G1 phase of the cell cycle, a feature associated with programmed cell death. Moreover, the hybrids showed selectivity for tumor cells, with lower toxicity in normal cells, further reinforcing their potential as promising therapeutic agents. These results highlight tacrine as a versatile molecular structure for developing new bioactive molecules with applications in cancer therapy.

Costa Nunes et al.[248] investigated the antitumor potential of new tacrine derivatives in cellular models of glioblastoma multiforme, one of the most aggressive and therapy-resistant brain tumors. The tested compounds (designated 3a, 3b, 3c, 3e, 3f, and 3g) exhibited high selective cytotoxicity for SF295 and SF295-R tumor cells, which are resistant to temozolomide. The results demonstrated that the derivatives were capable of inducing cell death through apoptosis and necrosis, associated with the activation of caspases, loss of mitochondrial membrane potential, and the production of Reactive Oxygen Species (ROS).

In addition to the derived compounds presented in Table 1, many studies are exploring new acridine derivatives, such as the studies by Almodarresiyeh et al.,[13] who synthesized the derivatives AD1 and AD2, 10-hydroxy-9-(4-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione and 10-hydroxy-9-(4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione, respectively. They evaluated the complete optimization of geometry, spectral analysis, electronic properties, and energy gap using the B3LYP method. It is worth highlighting that computational studies based on Density Functional Theory (DFT) and other methods can be used to calculate the global reactivity, predict the reactivity of system, and calculate the electronic and structure properties.[249-251]

Thus, the authors found that the synthesized acridine derivatives exhibit antioxidant activity and can be used for the development of anticancer drugs. It is worth mentioning that Lerman's study was the first to propose intercalation as an explanation for the strong affinity of certain heterocyclic aromatic dyes, such as acridine, to DNA.[10,193]

Despite the numerous advantages presented by acridine and its derivatives, as extensively discussed in this review, the application of these compounds is still limited by several issues, such as side effects, drug resistance, and low bioavailability.[236]

Proflavine has limitations and challenges for its safe use, mainly due to its toxicity and mutagenic properties. Despite its DNA intercalating ability, which contributes to its antimicrobial activity, it can also induce mutations and genetic damage in human cells, increasing the risk of carcinogenicity. Furthermore, it exhibits low bioavailability, drug resistance, and side effects, which limits its clinical use. However, studies and approaches such as the use of controlled release systems with biocompatible polymers, like Polyethylene Glycol (PEG), have shown promise in reducing toxicity, increasing selectivity, and improving the stability of the molecule.[236,237,239]

The real mechanism of action of drugs in cancer chemotherapy is complex and the study of intercalators and their derivatives, such as acridine, is necessary to increase the therapeutic perspective. Therefore, computational studies may prove beneficial in such cases. Research on the interaction with DNA/acridine and its derivatives is of immense importance and highly informative.[252] In this context, Miranda et al.[253] theoretically evaluated how acridine intercalation occurs with DNA. The authors showed that intercalation occurs through π-π interactions, and by hydrogen bonds with bond lengths ranging from 2,370 Å to 3,472 Å. The Quantum theory of atoms in molecules and non-covalent interactions characterized the interactions as being non-covalent in nature or van der Waals interactions.

7. Recent advances and future directions

Alternatives that seek better treatment for cancer have been studied and some deserve to be highlighted.

(i) Derivatives of nitrogenous bases: Molecules such as derivatives of uracil or other nitrogenous bases are often explored as potential precursors for synthesizing compounds with pharmacological applications.[254-260] The special interest in nitrogenous base derivatives with various substituent groups stems from their clinical potential and the possibility of generating a range of nucleobase derivatives to identify compounds with significant antiproliferative activity for cancer treatment.[254-260]

(ii) Long non-coding RNAs (lncRNAs), a family of RNA molecules with over 200 nucleotides, play an important role in cancer research. Some lncRNAs can act as oncogenes, promoting the onset and progression of cancer, while others function as tumor suppressors. Since their discovery, research has focused on identifying malfunctioning lncRNAs to associate them with anticancer therapies.[261-263] For example, Nuclear Enriched Abundant Transcript 1 (NEAT1) is a notable lncRNA that shows significant expression in various cancer types, including breast, gynecologic, lung, esophageal, colorectal, hepatocellular, and endometrial cancers.[261,264]

(iii) Metallopharmaceuticals: The study of metals in biological systems, particularly metallopharmaceuticals, offers promising treatment perspectives.[265] Metals such as silver and platinum, which have been recognized for their antimicrobial and cytotoxic properties for centuries, are promising candidates for synthesizing complexes with antiproliferative properties.[265-270] Combining metals with pharmacologically active molecules can enhance the properties of chemotherapeutic agents, such as improving solubility, selectivity, reducing side effects, and increasing efficacy. This approach also addresses the issue of multidrug resistance in tumor cells.[271] For instance, silver and platinum metal complexes with bioactive molecules have shown promising results in terms of antiproliferative activity, offering insights into the in vitro interactions of these compounds with key biomolecules, such as proteins and DNA,[266] and have even led to the complete reduction of skin squamous cell carcinoma tumors in mice.[270]

(iv) Nanocarriers: Nanoparticles are gaining prominence in various strategic fields, with a particular focus on biomedicine.[272,273] These structures can encapsulate drugs and function as nanocarriers.[274,275] Their advantages include reduced toxicity, biocompatibility with the drug, extended drug circulation time, improved pharmacokinetics, resolution of solubility issues for insoluble drugs, protection against degradation, responsiveness to stimuli, and targeted drug delivery.[276,277] Shakeran et al.[278] demonstrated the potential of modified mesoporous silica nanoparticles as nanocarriers for methotrexate delivery. Methotrexate, when loaded onto these modified nanoparticles, enhanced cancer cell death compared to the free drug. Additionally, the adsorption of the nanoparticles onto cancer cell surfaces facilitated the pharmacodynamics of methotrexate, as indicated by the increased interaction between the nanocarried methotrexate and its target enzyme, dihydrofolate reductase.

Cellulose acetate nanocapsules containing upconversion nanoparticles, as studied by de Topel et al.,[279] were used to deliver the chemotherapy drug doxorubicin. The drug was adsorbed onto the surface of the nanocapsules due to weak electrostatic forces between the drug and the nanocapsules. In vitro, the release of the drug was significantly higher at pH values between 5.5 and 3.6. Although the nanoparticles were slightly toxic to the in vitro cell lines examined, encapsulation significantly reduced this toxicity.

(v) Computer Simulations: Developing medicines and therapies for cancer treatment is complex, time-consuming, and costly. To address these challenges, computer simulations have become essential tools in drug discovery, providing crucial insights and efficiency gains in the drug development process.[280] Among the methodologies used, quantum mechanical techniques are notable for evaluating electronic and molecular properties such as bond lengths, frontier molecular orbitals, total energy, dipole moment, band energy gap, absolute hardness, global softness, electronegativity chemical potential, and electrophilicity index. Molecular docking is another key method, which involves using docking algorithms to position small compounds within the active site of the target, aiming to identify the best conformations and orientations. Additionally, Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) studies can be performed to assess the pharmacokinetic properties of promising compounds, offering valuable insights into their potential as drug candidates.[2,280-283]

(vi) Natural and Manufactured Compounds: These compounds have demonstrated significant potential against various diseases, including metabolic syndrome, diabetes, cancer, and chronic inflammation.[284] Many compounds are well-known for their antioxidant, hepatoprotective, anti-inflammatory, and potential antiviral activities, as well as their ability to scavenge free radicals.[285-288] For instance, Biochanin A, a phytoestrogen isoflavonoid, exhibits neuroprotective and anti-cancer properties. Coenzyme Q10, naturally present in the body, helps scavenge free radicals and counteracts lipid peroxidation.[285-287] Kaempferol, a flavonoid found abundantly in various plants, along with its glycosylated derivatives, has shown a broad range of applications, including notable antitumor activities.[284]

8. Conclusion

The review provides a comprehensive view of the main structural and functional characteristics of DNA, as well as describes a timeline involving the process of carcinogenesis and advances in treatment. Physical, chemical and biological factors can cause carcinogenesis. Surgery, chemotherapy, and radiotherapy are the primary therapies used clinically to treat cancer but present some problems such as side effects, toxicity, drug resistance and recurrence.

Modern approaches to drug discovery have focused their studies on understanding how the interaction with the target site occurs. Anticancer drugs can bind to DNA through covalent and noncovalent interactions where the covalent bond chemically modifies the constituents of DNA, is irreversible, and occurs at the junction of the bases or in the phosphate group. Non-covalent interaction occurs through groove binding, electrostatic binding with the sugar-phosphate structure, and by intercalation, which causes changes in the DNA conformation.

Among the class of intercalators is acridine, which exhibits important properties and aspects that indicate its potential as an anticancer drug. This is because it intercalates between DNA base pairs, altering the conformation, destabilizing its structure, and compromising the function of the nucleic acid. The intercalating activity of acridine has been studied for years. However, current research is mainly focused on its derivatives, and there are few current reports about this precursor molecule.

It is hoped that this work will encourage future research and clinical studies on acridine, its derivatives, and other mentioned intercalators or other compounds, thereby contributing to significant advancements in the development of new cancer treatments.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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