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Antisense oligonucleotides: recent progress in the treatment of various diseases

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Abstract

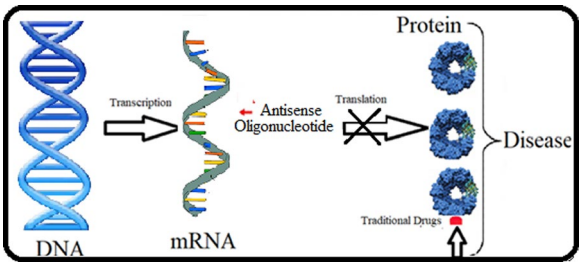
Background: Antisense oligonucleotides are a promising novel class of therapeutic agents to treat different diseases in living things. They provide an efficient method for making target-selective agents because they change gene expression sequences. Therefore, the malfunctioning protein could be stopped, and the source of disease would be obliterated. The existing reviews of antisense oligonucleotides are focusing on discovery, development and concept. However, there is no review paper concerning the latest development of antisense oligonucleotides and their different therapeutic uses. Therefore, the present work has been targeting a comprehensive summary of newly synthesized antisense oligonucleotides and their biological activities.

Main body: Antisense oligonucleotides are different from traditional therapeutic agents that are planned to interact with mRNA and modulate protein expression through a unique mechanism of action. In the last three decades, several researchers revealed the newer antisense oligonucleotides found with a high therapeutic profile due to more selective action on the drug target and thus producing a lesser side effect and low toxicity. This review emphasizes the research work on antisense oligonucleotides and their therapeutic activities.

Short conclusion: With the support of the literature review, here we enlisted various antisense oligonucleotides that were prepared by appropriate technique and explored their pharmacological activities. To the best of our knowledge, it is the right time to consider the antisense oligonucleotides as a perfect choice of treatment for different diseases due to conceptual simplicity, more selective action, lesser side effects, low toxicity and permanent cure.

Keywords: Antisense oligonucleotides, Target-selective, Treatment, Permanent cure, Various diseases

Graphical abstract



1 Background

Antisense oligonucleotides (ASOs) are accepted widely as potential therapeutics agents for different diseases in human beings [1–3]. It was discovered over 40 years ago, which resulted in modern tools of genomics and

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proteomics [4]. ASOs are different from traditional drugs that are considered to interact with mRNA and modulate protein expression through a different mechanism of action [5]. Therefore, the malfunctioning protein could be stopped, and the source of disease would be obliterated. This idea is the basic concept of antisense technology [6]. This method was successfully used in plants to change the level of different degradative enzymes and colouring agents [7]. Later, the technology was rapidly applied to mammalian cells in 1992 [8]. Antisense oligonucleotides are being researched in human to treat various diseases [9–13]. It shows more selective action on the target and thus produces a lesser side effect, low toxic than the traditional drugs [14, 15]. In the last three decades, many researchers revealed the novel antisense oligonucleotides found with a high therapeutic profile. But there is no review relating to the latest research discoveries of antisense oligonucleotides. Hence, an effort had been made on the latest finding of newly synthesized antisense oligonucleotides for the treatment of various diseases. To the best of our knowledge, the review has completely examined the newer antisense oligonucleotides including concept, design, method of preparation, mechanism of action, and the effect of these agents against different chronic diseases (Fig. 1).

2 Main text

2.1 Design of antisense drug

The design of antisense oligonucleotide strand is easy, but it should fulfil many conditions such as

1. Antisense oligonucleotide molecules should not be degraded by the nucleases enzyme.
2. It must have a molecular structure opt for binding with target mRNA.
3. It initiates the biomolecular reactions in the target mRNA as soon as it is attached to them [16].

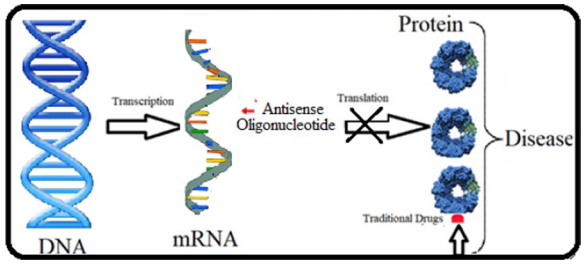

Fig. 1 Concept of antisense drug technology

2.2 Methods of preparation of antisense oligonucleotides

To make antisense drugs, chemically stabilized nucleotides are linked together in short chains [17]. The methyl phosphonate backbone yields molecules that are non-ionic and form a stable duplex with mRNA. The duplex formed is degraded by nucleases. The first successful backbone chemistry that modified the phosphodiester is phosphorothioate linkage [18]. The resulting compound is the broadest range of activities in which the oxygen atom is replaced by sulphur in the phosphonate group. The obtained molecule has chiral, negative charged, nuclease resistance and form a stable duplex with mRNA. The major drawback of phosphorothioates is a low concentration of drug in plasma, less attraction for their target mRNA and side effects such as clotting abnormalities and immune stimulation [19]. The second-generation molecules (2'-O-methoxyethyl or 2-MOE) are composed of both DNA- and RNA-like nucleotides. These compounds provide therapeutic effects at lower doses. They significantly slow down the degradation of the drugs by protecting the drug from destructive nucleases [20]. Third-generation drugs were developed by chemically modifying the furanose ring of the antisense oligonucleotides, along with modifications of phosphate linkages or of riboses, as well as of nucleotides [21]. They were made to improve the nuclease stability, target affinity and pharmacokinetic profiles of the antisense oligonucleotide. Locked nucleic acid (LNA), peptide nucleic acid (PNA) and morpholino phosphoroamidates (MF) are the three most commonly used third-generation antisense oligonucleotides [22]. The different antisense oligonucleotides are shown below (Fig. 2).

2.3 Mechanism of action

Antisense drugs are designed with a suitable harmonizing genetic code to bind a specific sequence of nucleotides present in the target mRNA and interfere with the production of abnormal proteins. Therefore, malfunctioning protein could be stopped, and the source of disease would be obliterated. In addition, comprehensive studies acknowledged that the action of synthetic ASOs could be RNA cleavages and RNA blockage [23].

2.4 Clinical application of antisense oligonucleotides:

Antisense drugs are being researched to treat hemorrhagic fever, HIV/AIDs, amyotrophic lateral sclerosis, cardiovascular disease, diabetes, obesity, renal disease, asthma, inflammation, arthritis, spinal muscular atrophy, Duchenne muscular dystrophy, cystic fibrosis and cancer diseases [24–27]. These diseases are currently being addressed by antisense oligonucleotides and will hope to target the new potential therapeutic compounds

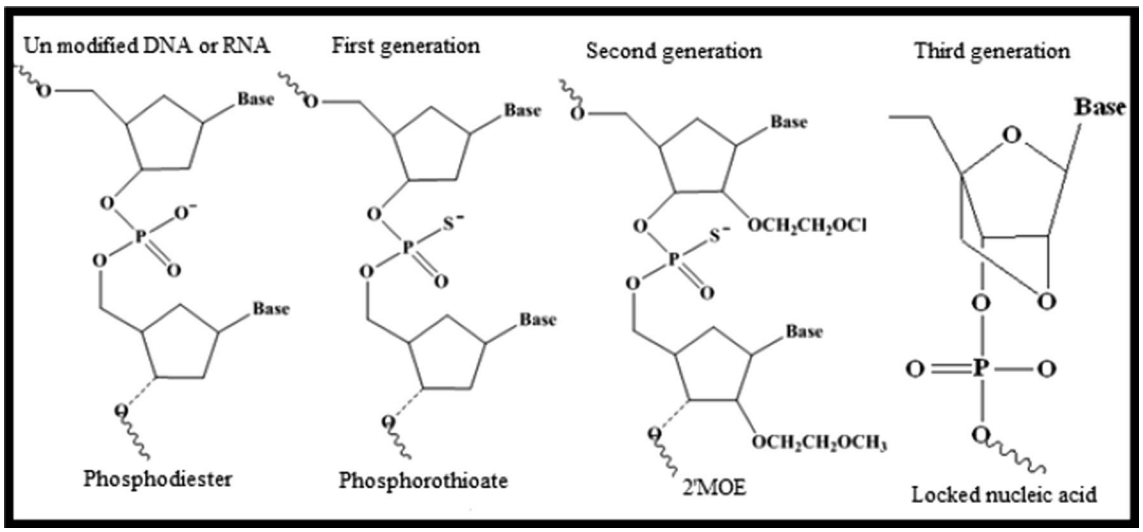

Fig. 2 Different generations of antisense drugs

for many diseases. However, the minimum use of ASOs in the treatment of disease requires effective design and specificity. Some of the optimal use of antisense oligonucleotides has been mentioned here (Fig. 3).

2.4.1 Antiviral agents

Burrer and co-workers reported the antiviral activity of novel phosphorodiamidate antisense morpholino oligomers (P-PMOs) in mouse models infected with murine hepatitis virus (MHV). They utilized different strains of virus in cell culture and evaluated the effect of P-PMOs in tested models in vivo. There are ten P-PMOs engaged against different target mRNA genomes that were tested in culture. The result reveals that one of these molecules called 5TERM PMO perfectly complementary to the virus genomic RNA. Therefore, the mentioned PMO was effective against 6 different strains of murine hepatitis virus. In addition to that, the authors performed various arginine-rich peptides conjugated to the 5TERM PMO sequence to calculate potency and toxicity, in that way they selected appropriate PMO for in vivo testing. The selected compound inhibits viral titres in the organs of mice and saved against the different tissue damages [28].

Chadwick et al. narrated that antisense RNA has been recognized as a powerful inhibitor of gene expression and prevents retroviral replication at different phases in virus life cycle. The novel antisense RNA drug was complementary to 3 target regions in the 5' leader of HIV-1. They are TAR region, the splice donor packaging signal region, the primer binding site and were confirmed by RT-PCR. The result unveils that the packaging signal (ψ) of HIV-1 is an attractive target for ASOs therapy [29].

Kobayashi–Ishihara et al. found that latently infected T lymphocytes are a vital barrier towards reducing persistent HIV. The authors describe that an HIV-based recombinant fluorescent lentivirus (rfl-HIV) enables to notice antisense and sense transcription of the virus using fluorescence genes. Hence, rfl-HIV transcripts can display the core suppressor activity and be able to lock an incorporated provirus into a non-functional condition.

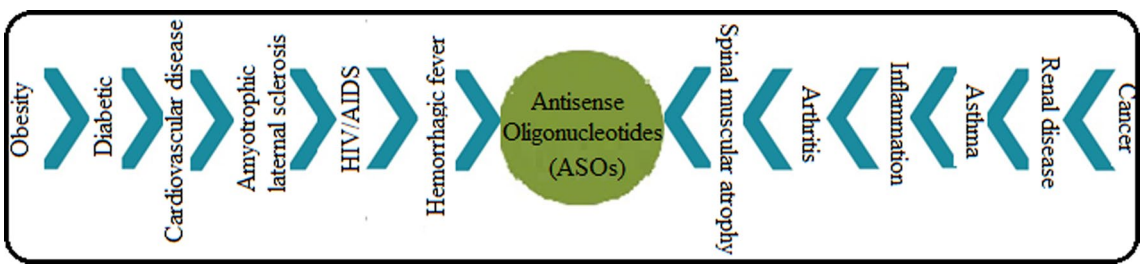

Fig. 3 Application of antisense drugs

Therefore, it is a significant step to eliminate HIV from infected individuals [30].

Markov et al. prepared chemically modified ANOs against influenza A virus such as (H1N1)/MDCK and (H1N1)/A549. The result has revealed that PB1-2AUG-R ANOs targeted AUG codon of virus nucleic acid genome gained the maximum activity. The synthesized morpholino analogue (PMO) and the novel phosphoryl guanidine oligodeoxyribonucleotide (PGO) offered a worthy effect against the influenza virus. The virus was inhibited by fifteen times, while PGO was utilized at 10 μM concentration and by forty times when PMO was employed at 20 μM concentration compared with control [31].

Offensperger et al. reported antisense treatment of duck hepatitis B virus (HBV) disease by blocking gene expression. To test this activity, Peking ducks were used and infected the duck with hepatitis B virus (DHBV). An antisense oligodeoxynucleotide used against the 5'-region of the preS nucleic acid gene of DHBV. The mechanism of action of ASOs-controlled gene expression and viral replication have been identified through in vitro and in vivo studies. The authors concluded that the clinical use of antisense as antiviral therapeutic agents [32].

Putlitz et al. described a novel antisense RNA complementary that has considerable antiviral activity against hepatitis B virus (HBV). Here, the authors assessed the effectiveness of antisense drug molecules based on the interference with HBV replication. In the initial stage of the work, subgenomic fragments of HBV were studied for an effective making of antisense drug molecules. Here, the RNA-based antisense inhibited the HBV replication and antigen formation in human hepatocellular cancer cells by up to 70%. Therefore, RNA-based antisense drugs have extensive potency and may serve as a new technique to treat HBV infection [33].

Zhu et al. found that short antisense oligonucleotides called LNA-YN8-A and LNA-YN8-B inhibit porcine reproductive and respiratory syndrome virus (PRRSV) replication by locked nucleic acid modification. These drugs are modified with LNAs at both ends such as mixmer and gap-mer. PAMS or Marc-145 cells were infected with PRRSV and subsequently transfected. The results were compared with DNA-based YN8 control. Both the antisense drugs were found to be more helpful in diminishing the cytopathic effect caused by PRRSV and thus in maintaining cell viability. The addition of LNA into antisense oligonucleotide technology sets a higher therapeutic effect compared to the existing drugs [34].

2.4.2 Antidiabetic agents

Liang et al. carried out a novel handling of type 2 diabetes by using gene therapy. The study illustrates the effects of a specific antisense oligonucleotide (GR-ASO) in the mice model. These drugs inhibit glucagon receptor mRNA expression and were confirmed by a quantitative real-time RT-PCR test. The antisense drug was administered through intraperitoneal (IP) route at a dose of 25 mg/kg two times a week in mice for 21 days resulted in reduced GR mRNA expression in the liver, extensively reduced blood glucose, free fatty acids, triglyceride and reduced glucagon stimulated cAMP intervention in hepatocytes isolated from tested animals were absorbed. In addition to that, the antisense drug also enhanced glucose tolerance and reduced hyperglycaemic response to glucagon challenge [35].

In another report, the author evaluated that non-obese diabetic mouse dendritic cell (NOD) bone marrow-derived DCs intending to avoid diabetes in syngeneic recipients by Machen et al. The low surface CD40, 80 and 86 cells were exclusively regulated by treating NOD DCs ex vivo with a combination of antisense oligonucleotides. Engineered DC encouraged an increased occurrence of $CD25^+$ and $CD4^+$ T cells in NOD recipients at all age groups studied, and diabetes-free recipients exhibited greater numbers of $CD25^+$ and $CD4^+$ T cells compared with untreated NOD mice. Therefore, the occurrence of diabetes was considerably postponed by a single-dose administration of the engineered NOD DCs into syngeneic recipients [36].

Oshitari et al. reported the outcome of combined antisense oligonucleotides against elevated sugar levels, diabetes-induced overexpression and increased vascular permeability was identified in rat microvascular endothelial cells (RMECs). Our result shows the combined AS-oligonucleotide approach is useful in simultaneously dropping laminin overexpression, fibronectin, collagen IV expression and decreasing vascular leakage in the retinal capillaries in the tested rats. The decision strongly recommended that the unusual level of ECM components may give vascular outflow in the diabetic retina [37].

Sloop et al. found that setback of diabetes by glucagon receptor antisense oligonucleotide (GCGR ASOs). The rodents were utilized to determine the level of blocking effect of glucagon receptor (GCGR). Here, the experimental animals were treated with a 2-methoxyethyl-modified phosphorothioate ASO. The effect of GCGR ASOs reduced GCGR expression, regulated blood glucose, preserved insulin secretion and improved glucose tolerances, notably reducing the expression of cAMP-regulated genes and avoiding glucose production in the liver. Moreover, GCGR reserve improved blood concentrations of active glucagon-like peptide-1 and insulin levels in pancreatic islets [38].

2.4.3 Anti-arthritic agent

Akhavein and coworkers examined the effect of microencapsulated antisense oligonucleotides as a potent healing agent employed to selectively reduce nuclear factor-kappa B (NF-kB), which acts as a vital transcription factor in the inflammatory condition. The study suggested that there is a considerable inhibition of NF-kB after treating with microencapsulated antisense oligonucleotides. Therefore, it can be suggested as a potential treatment in the pathogenesis of inflammation [39].

A novel method of treatment of ASOs for a reserve of ADAMTS in co-delivered and resident joint cells in osteoarthritis by Garcia et al. The ADAMTS enzyme is responsible for the loss of proteoglycans during cartilage deterioration in osteoarthritis. Locked ASOs released from biomaterial scaffolds for specific and prolonged ADAMTS inhibition in co-delivered and resident chondrocytes. Inclusion of the gapmer is a fibrin-hyaluronic acid hydrogel that displayed a delayed-release profile for up to 2 weeks. The effective knockdown of ADAMTS5 was exhibited up to 2 weeks in gapmer loaded and gapmer-free hydrogel [40].

Makalish et al. discussed the effect of antisense oligonucleotide Cytos-11 inhibiting TNF-α gene expression in a rat model. The Cytos-11 ASOs has been shown a potent suppression of TNF-α expression for joint inflammation, peripheral blood concentrations and reduce pannus development. The obtained results were compared to adalimumab [41].

Morita et al. were reported the inhibition effect of rheumatoid synovial fibroblast growth by ASOs. The fibroblast cells secreted interleukin-1β responsible for rheumatoid arthritis (RA). Interleukin-1β has been treated with ASOs by targeting messenger RNA. Both mRNA and protein levels of proliferating cell nuclear antigen were concealed in the cell treated with antisense oligonucleotides, demonstrating that the antiproliferative effect was attained through a novel method of treatment [42].

Hildner et al. demonstrated that the transcription factor STAT4 induced arthritis which was treated effectively by novel antisense oligonucleotides (ASPOs). The STAT4 factor is responsible for creating signals to different proinflammatory cytokines such as IL-12, IL-23 and IL-15 that commence and stabilize the production of Th1 cytokine. A specific ASPOs focused on the translation site and reduced STAT4 levels and signs of CIA even when applied during the onset of disease symptoms [43].

In vitro and in vivo studies of antisense oligonucleotide were performed for targeted delivery to tissues and cells by Nakamura et al. ASOs are able to bind specific gene regions and control protein translation, they are helpful to avoid abnormal endogenous processes connected with a particular illness such as dyslipidaemia and hepatitis. Here, the author targeted potential roadblocks in the particular clinical translation through ASO-based therapies for the management of osteoarthritis. The stage is set with the ongoing surge in human genomic and proteomic data that will enable the detection of promising RNA targets for ASOs [44].

2.4.4 Anti-inflammatory agent

A multi-target antisense technique has been used against PDE7 and PDE4 decline smoke-induced respiratory inflammation in mice by Fortin et al. This study revealed that the effect of 2'-deoxy-2-Fluoro-β-D- arabinonucleic acid (FANA)-containing ASON targeting the messenger RNA of PDE4B, of PDE 4D and PDE 7A subtypes of pulmonary inflammatory markers. When used in combination ASONs, drastically abrogated the cytokine-induced discharge to near baseline levels. Therefore, the experimental animals treated with combined AONs and exposed to cigarette smoke, considerable inhibition of target mRNA in cells from lung lavages [45].

Karras et al. found the anti-inflammatory effect of inhaled IL-4 receptor-α antisense oligonucleotide (IL-4RA) in mice models. The Th2 cytokines called IL4 and IL13 cause allergic lung inflammation as well as airways hyperreactivity (AHR) in asthma. The mentioned receptor-lacking mice are opposed to allergen-induced asthma, which stress the healing effect of selective inhibitors. The authors designed a chemically modified IL-4RA that specifically reduces IL-4Rα protein expression in lung eosinophils, dendritic cells, macrophages and airway epithelium following inhalation in allergen challenged mice. The experimental results support the possible utility of IL-4RA in asthma/allergy [46].

Ramelli et al. found a novel drug delivery of LNA oligonucleotides that curbs airway inflammation in a HDM model. During the literature study, an ASO preventing mmu-miR-145a-5p was estimated in a mouse model for mild-moderate asthma. ASOs in the form of nanoparticles dispersed to the majority of cells in the lung but were not there in the smooth muscle of the upper respiratory tract. Therefore, they reduced obstructive airway remodelling, mucosal metaplasia, eosinophilia and CD68 immunoreactivity. The result reveals that the nanoparticles were delivered in the lungs and treated pulmonary inflammation due to the normalization of interferon pathways [47].

Donner et al. described that a new method of treatment for doxorubicin-induced nephropathy and renal inflammation through antisense oligonucleotides. The data obtained from preclinical and clinical suggested the activation of CD40 gives to nephropathy, renal injury and inflammation. The inhibition of renal CD40 expression is

a novel way to treat injury and unilateral ureter obstruction in mouse models. Here, experimental animals were administered with 2.5 CD40 ASO inhibiting CD40 mRNA levels between 75 and 90% in the renal organ. Therefore, this study recommends strongly CD40 ASO as an effective therapy in doxorubicin-induced nephropathy, renal inflammation and injury [48].

Zorzi et al. investigated a new method of treatment for inflammatory bowel disease using Smad7 antisense oligonucleotide (ASOs). Transforming growth factor-β1 (TGF-β1) is a potent director of numerous mucosal inflammation in the gut and other parts of the body. Here, Smad7 antisense oligonucleotide inhibiting TGF-β1 has been documented in inflammatory bowel disease (IBD). These findings demonstrate that Smad7 ASOs is safe and well tolerated in patients with Crohn's disease [49].

2.4.5 Anticancer agents

Vanderborght et al. described the effect of antisense oligonucleotides (HIF-1α and HIF-2α) on tumorigenesis, fibrosis and inflammation in a mouse model. Hepatocellular carcinoma (HCC) is naturally associated with the hypoxia-inducible factor (HIF) that acts a vital role in HCC growth and development. Hence, the author examined the therapeutic action of isoform-specific HIF-1α and HIF-2α ASOs on the tumorigenesis, fibrotic and inflammatory components of the tumour microenvironment. The results discourage the use of both isoforms of HIF-1α and HIF-2α ASOs as targets for the treatment of hepatocellular carcinoma [50].

Abaza et al. reported c-myc antisense oligonucleotides used to treat human colon tumour and carcinoma. We learned the process of making the sensitivity of human colorectal cancer cells using c-myc antisense phosphorothioate oligonucleotides ([S]ODNs) with chemotherapeutic drugs such as 5-fluorouracil(5FU), taxol, vinblastine and doxorubicin either alone or in combination. After administering of c-myc AS[S]ODNs alone, the development of tumour cells was inhibited considerably ($p < 0.006$) and levels of protein and c-myc mRNA were significantly reduced. The combinations of chemotherapy exhibited time and dose-dependent additive and/or synergistic antitumour properties. Here, cells treated with either c-myc AS[S]ODNs alone or in the combination with cytotoxic drugs were arrested the cell growth in G2/M and S Phase. The combination of treatments also showed a noticeable apoptotic effect compared to a single treatment [51].

A recently published article reported that an antisense oligonucleotide drug (ASOs) targeting miR-21 induces H1650 apoptosis by Ge et al. MicroRNAs have been considered as a vital role in the progression of many tumours. Here, five molecules of oligonucleotides were designed, synthesized and identified for antitumour activity. The suggested antisense oligonucleotides target microRNAs by gene silencing. Among these five antisense oligonucleotides, phosphorothioate oligonucleotide 4 inhibited the proliferation of H1650 cells due to the stimulation of apoptosis by triggering the caspase 8-apoptotic pathway [52].

Ciardiello et al. found the reserve of bcl-2 as tumour therapy. Antisense oligonucleotides bind to particular mRNAs and control the endogenous expression of genes. Therefore, tumour development and progression could slow down the tumour cell. Here, ANOs bind to the target messenger RNA by Watson–crick base-pairing resulting in the reserve of mRNA translation into protein [53].

A recently published article reported that a phase I/II clinical study of antisense oligonucleotides (LY900003) against cancer treatment by Villalona-Calero et al. It inhibits protein kinase C-*α*, with a combination of gemcitabine and cisplatin in patients with advanced non-small cell lung cancer (NSCLC). The protein kinase C-α is involved in malignant transformation and development. The mentioned ASOs with the combination of existing chemotherapeutic agent ensure the safety and requisite pharmacokinetic interactions were evaluated in phase I clinical trials. There are no significant adverse effects seen in any of the patients. In phase II, the combination of dose with gemcitabine and cisplatin was given and assessed anticancer activity in patients with advanced NSCLC [54]. Finally, the author concluded that LY90003 can be administered safely along with the existing chemotherapeutic agents and has shown excellent action against cancer cells. The literature search and original articles for the use of antisense oligonucleotide therapy are summarized below (Table 1).

3 Conclusions

Although still in infancy, the successful manipulation of antisense technology has been a significant breakthrough and exhibits the potential of this approach as a new therapeutic strategy. Several in vitro and in vivo experiments on ASOs has increased constantly and led to many therapeutic trials, some of them now appear preliminarily to provide better treatment of various diseases for the last three decades. With the support of the literature review, here we enlisted various antisense oligonucleotides that were prepared by appropriate technique and explore their pharmacological applications. It is the right time to think of this approach because of more selective action on the target, lesser side effects and low toxicity. To the best of our knowledge, this review has entirely analysed the complete information

Table 1 A summary of therapeutic applications of antisense oligonucleotides

S. no	Author's	Molecule	Mechanism of action	Therapeutic uses
Antiviral agent				
1	Burrer et al. [28]	Phosphorodiamidate antisense morpholino oligomers (P-PMOs)	Inhibiting mRNA genome	Inhibiting murine hepatitis virus (MHV)
2	Chadwick et al. [29]	Antisense RNA	Inhibitor of gene expression and prevent retroviral replication	Anti-HIV-1
3	Kobayashi-Ishihara et al. [30]	Latently infected T lymphocytes	Inhibiting HIV transcription	Anti-HIV
4	Markov et al. [31]	Phosphoryl guanidine oligodeoxyribonucleotide (PGO)	Inhibiting AUG codon of virus nucleic acid genome	Anti-influenza A virus
5	Offensperger et al. [32]	Antisense ANOs	Gene expression and viral replication	Anti-hepatitis B virus
6	Putlitz et al. [33]	RNA based antisense oligonucleotide	Inhibited the HBV replication and antigen formation	Anti-hepatitis B virus (HBV)
7	Zhu et al. [34]	LNA-YN8-A and LNA-YN8-B short antisense oligonucleotides	Diminishing the cytopathic effect	Against respiratory syndrome virus
Antidiabetic agents				
8	Liang et al. [35]	GR-ASO	Reduced GR mRNA expression in the liver	Antidiabetic agent
9	Machen et al. [36]	Non-obese diabetic mouse dendritic cell (NOD DCs) antisense oligonucleotides	An increased occurrence of $CD25^{+}$, $CD4^{+}$ T cells	Antidiabetic agent
10	Oshitari et al. [37]	Combined AS-oligonucleotide approach	Laminin overexpression, fibronectin, collagen IV expression and decreasing vascular leakage in the retinal capillaries in the tested rats	Antidiabetic agent
11	Sloop et al. [38]	Glucagon receptor antisense oligonucleotide (GCGR ASOs)	Avoid glucose production in the liver	Antidiabetic agent
Anti-arthritic agent				
12	Akhavein et al. [39]	Microencapsulated antisense oligonucleotides	Reduce nuclear factor-kappa B (NF-kB)	Anti-arthritic agent
13	Garcia et al. [40]	Locked ASOs	Inhibition of ADAMTS enzyme	Anti-arthritic agent
14	Makalish et al. [41]	Cytos-11 ASOs	Inhibiting TNF-α gene expression	Anti-arthritic agent
15	Morita et al. [42]	ASOs	Inhibition effect of rheumatoid synovial fibroblast growth	Anti-arthritic agent
16	Hildner et al. [43]	Antisense oligonucleotides (ASPOs)	Inhibition of STAT4 factor	Anti-arthritic agent
17	Nakamura et al. [44]	ASOs	Control protein translation process	Anti-arthritic agent
Anti-inflammatory agent				
18	Fortin et al. [45]	2′-Deoxy-2-fluoro-β-D- arabinonucleic acid (FANA)-containing ASON	Inhibition of PDE7 and PDE4 enzyme	Anti-inflammatory agent against smoke-induced respiratory inflammation
19	Karras et al. [46]	Inhaled IL-4 receptor-α antisense oligonucleotide (IL-4RA)	Inhibition of IL4 and IL13 cytokines	Anti-inflammatory agent against lung inflammation
20	Ramelli et al. [47]	LNA oligonucleotides	Preventing the formation of mmu-miR-145a-5p	Anti-inflammatory agent
21	Donner et al. [48]	2.5 CD40 ASO	Inhibiting CD40 mRNA expression	Anti-inflammatory agent
22	Zorzi et al. [49]	Smad7 antisense oligonucleotide (ASOs)	Inhibiting growth factor-β1 (TGF-β1)	Inflammatory bowel disease
Anticancer agents				
23	Vanderborght et al. [50]	HIF-1α and HIF-2α antisense oligonucleotides	Inhibiting hypoxia-inducible factor (HIF)	Hepatocellular carcinoma
24	Abaza et al. [51]	c-myc antisense oligonucleotides ([S]ODNs)	Inhibiting c-myc mRNA and proteins	Colon tumour and carcinoma
25	Ge et al. [52]	Antisense oligonucleotides targeting microRNAs	Inhibiting miR-21, induces H1650 apoptosis	Antitumour
26	Ciardiello et al. [53]	Antisense oligonucleotides	Control the endogenous expression of genes	Antitumour

Table 1 (continued)

S. no	Author's	Molecule	Mechanism of action	Therapeutic uses
27	Villalona-Calero et al. [54]	LY900003 antisense oligonucleotides	Inhibits protein kinase C-α	Anti-lung cancer

of antisenses such as discovery, concepts, design, method of preparation, mechanism of action and recent progress in the treatment of various diseases.

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Abbreviations

ASOs: Antisense oligonucleotides; mRNA: Messenger ribonucleic acid; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; HIV: Human immunodeficiency virus; P-PMOs: Peptide-conjugated antisense phosphorodiamidate morpholino oligomers; PMO: Phosphorodiamidate morpholino oligomers; CMV: Cytomegalovirus; H1N1: Hemagglutinin type 1 and neuraminidase type 1; PGO: Phosphoryl guanidine oligodeoxyribonucleotide; MDCK: Madin-Darby canine kidney; DHBV: Duck hepatitis B virus; HBV: Hepatitis B virus; PRRSV: Porcine reproductive and respiratory syndrome virus; LNA: Locked nucleic acid; PAMs: Pulmonary alveolar macrophages; GR-ASO: Glucagon receptor antisense oligonucleotide; cAMP: Cyclic adenosine monophosphate; CD 40,80,86: Cluster of differentiation 40, 80, 86; RMECs: Rat microvascular endothelial cells; GCGR: The human glucagon receptor; NF-kB: Nuclear factor-kappa B; ADAMTS: Disintegrin and metalloproteinase with thrombospondin motifs; TNF-α: Tumour necrosis factor-alpha; STAT4: Signal transducer and activator of transcription 4; IL: Interleukin; FANA: 2′-Deoxy-2-fluro-β-D- arabinonucleic acid; Th2: T helper cell type 2; HDM: Hidden dynamic model; TGF-β1: Transforming growth factor-beta 1; HCC: Hepatocellular carcinoma; HIF: Hypoxia-inducible factor; [S]ODNs: Phosphorothioate oligonucleotides; miR21: Small regulatory RNA microRNA-21.

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Authors' contributions

CG designed the study and write the whole manuscript. MDD and KD contributed to the major work in analysing the data and structured the manuscript in a journal format. All the author read and approved the final manuscript.

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Availability of data and materials

All the data generated and analysed during the study are included in the manuscript.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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