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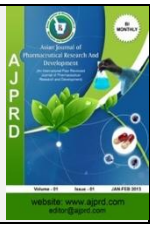

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Review Article

Aptamer as a Targeted Drug Delivery

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A B S T R A C T

Aptamers are the synthetic oligonucleotides which are short single-stranded in nature with having three-dimensional shape or structure. From the past few years, Aptamers as inventive targeting molecules play an important role in the biomedical field. Aptamers are generated by the method termed as SELEX. Aptamers have a unique feature in which they bind to the desired targets or the receptors on the cell membrane utilizing their high affinity and specificity. So, for drug delivery as targeting ligands, aptamers can be provided. In the research field, for monitoring the environment and ensure the food safety aptamers are generally used. They also used as a therapeutic agent and plays an important role in clinical diagnosis. An Aptamer is a fascinating tool that is mainly used in molecular biology applications, as well as potential pharmaceutical agents and the reason behind this fascinating tool, is the various unique properties of the aptamer. Aptamers have more advantages over antibodies. They can be selected against bacteria and viruses. This review provides an overview of the development of Cell-Specific aptamers for targeted drugs along with the advantages, uses, and applications of aptamers.

Keywords: - Aptamer, SELEX, Targeted Drug Delivery, Antibodies, Cell-specific.

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INTRODUCTION:-

Aptamers are the synthetic oligonucleotides that are short, single-stranded in nature possess specific three-dimensional shape or structure that are prescribed by their sequence which having the high capability and specificity to bind with a target molecule's are usually developed via in vitro process by ceaseless screening process of complex nucleic acid libraries that process termed as Systemic Evolution of Ligands by Exponential Enrichment (SELEX) given by Turek and Gold in 1990 which aims to find an RNA aptamer sequence that would bind T4 DNA polymerase[1].SELEX is a revolutionary process, includes successive rounds of selection and amplification for enriching the aptamer library for high affinity aptamer. So, employing SELEX candidates are screened and characterized which further used in different types of applications. Mainly the applications range from therapeutic uses to biosensors for target detection[2]. Aptamers have extraordinary advantages over Antibodies. Aptamer contains not only genotypic but also phenotypic properties that are capable of hereditary in vitro selection [3].

In the new level of aptamer applications, Aptamer heightened against membrane receptors have been exploited as targeting agents and carriers for delivery of a variety of reagents to specific the type of cell tissues[4]. Aptamers increase the accumulation of therapeutic agents by the specific interaction between the aptamer and its receptor of the cellular membrane. Utilizing receptor-mediated endocytosis cellular intake was allowed by the internalization of aptamer so that the drug's local concentration in the targeted cells or tissues increased. Whereas entrapment in endocytic vessels and successive endosomal release is the major drawback for the application

of aptamer as drug delivery vehicles and because of this large-scale various activity are conducted for the improvement of efficiency of intracellular delivery by developing aptamer compatible endosomal strategies. For example, Aptamer which acts as environment-sensitive nanocarriers could facilitate the cellular uptake and increase endosomal release[5].

The Aptamer is a fascinating tool which is mainly used in molecular biology applications as well as potential pharmaceutical agents and the reason behind this fascinating tool is various unique properties of an aptamer such as (a) Maximum aptamer binds to the targets with demonstrating typical dissociation contrasts which includes the range from Pico to nanometer, with high specificity and affinity. Binding sites present for the aptamers contain cleft and grooves of target molecules with including enzymes can give antagonistic properties that are analogous to various currently available pharmaceutical agents.(b)For the production of monoclonal antibodies needed by work-intensive biological systems, aptamers can be synthesized chemically.(c)Beyond a broad range of temperature and storage conditions aptamers are structurally stable by maintaining the ability to form their unique tertiary structures.

In the research field, to monitoring the environment and ensure the food safety aptamers are generally used. They also used as a therapeutic agent and plays an important role in clinical diagnosis.

Like antibodies, aptamers recognize their target and binds to it. They pose no advantages like no batch to batch variability, high modifiability, shorter generation time, higher target potential and better thermal stability.

A comparison of the demanding features of aptamers shows that how aptamers can supplement monoclonal antibodies.

Table: 1 Advantage of Aptamers over Antibodies.

	APTAMERS	**ANTIBODIES**
Synthesis	In vitro process. SELEX takes near about 3-8 weeks. Synthesis is cheap.	In Vivo process. SELEX takes more than 6 months. Synthesis is expensive.
Synthesis method	enzymatic or chemical synthesis	By using cell culture or laboratory animals
Affinity	High.	Depends upon the no of epitopes present on the antigen.
Specificity	High	On the same antigen different antibodies can bind.
Kidney filtration	Rapid.	Slow.
Stability	High	Low
Shelf life	Long	Short
Size	Small molecules .	By comparison its relatively large.
Modifiability	Without reduced activity easily modify.	Modification often leads to activity reduction.
Target potential	From small molecules to whole-cell and live animal.	Target requires a strong immune response for the production of antibodies.
Targets	Wide range	Immunogenic molecules
Cost	Cheap	expensive at large scale

1.1 SYSTEMATIC EVOLUTION OF LIGANDS BY EXPONENTIAL ENRICHMENT:-

From a random single-stranded RNA/DNA sequence pool oligonucleotides can determine which is carried out through in vitro selection termed as SELEX which is developed in 1990 by two independent research groups. It is an in vitro way which determines binding affinities of drug, peptides, proteins and small molecules to either RNA or DNA. It is a constant screening process in which RNA, single-stranded or double-stranded DNA molecules are selected from a large pool of oligonucleotides of alternative sequences followed by numerous rounds of enrichment of bound oligonucleotides. The constant enrichment process poses elution of bound oligonucleotides and their consecutive amplification by means of Polymerase Chain Reaction (PCR) which results in a final product of nucleic acid aptamers. After the development of SELEX in 1990 better modifications and achievements were done in aptamer selection. Current SELEX method generally involves some steps like-

a) Selection of random library with targets
b) Separation of bound aptamers from unbound
c) Amplification by using PCR of bound sequences

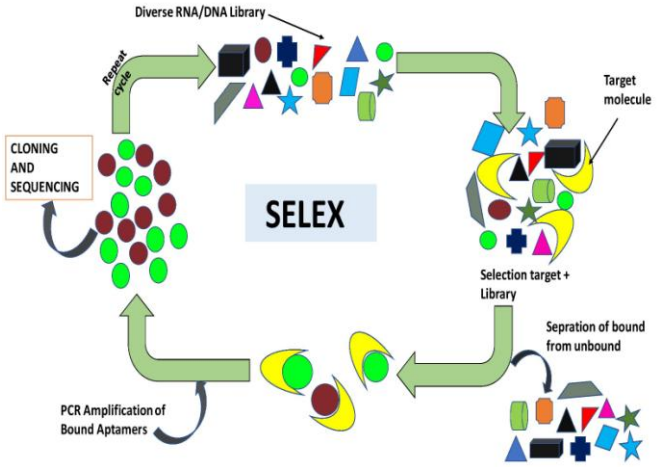

Figure: 1 Systematic Evolution Of Ligands By Exponential Enrichment (SELEX):-

To generate aptamers by using SELEX method oligonucleotide libraries (as nucleic acid) play an important role. Classical SELEX libraries are 10 – 10 molecules which have 20-70 long nucleotides. They follow a sequence of arrangements in 3 parts such as 3'– 5' sense primer sequence, random nucleotide, 3' antisense primer sequence parts respectively. Generally, 5' sense or 3' antisense sequence part of oligonucleotides library is 18-22 base long and in between 5' and 3' sequences there is the presence of random sequence which have a range from 20 to 40 nucleotides[6.]

Along with Classical libraries, various libraries also used for SELEX methods like Genomic sequences or free of fixed sequence, structurally modified, a sequence which is known. A library which includes 4-6 nucleotides having fixed regions on both sides used for SELEX termed as fixed of free sequence oligonucleotide library. (tailored SELEX)[7]. In Genomic SELEX genomic-based libraries are used. Furthermore, to examine sequences like translation regulators, splicing sequences, transcription factors Genomic SELEX is used. In this SELEX, on each region fixed sequences are present and the oligonucleotide libraries are consisting of 50 to 500 nucleotides[8].

Another one is structurally modified libraries in which a secondary structure (Hairpin, G-quartets, vs) is formed by building a random region between two fixed sequences for selecting more stable aptamers against the target molecule[9].

Certain modified SELEX methods are set up with respect to research goals such as – Affinity Chromatography and magnetic-based SELEX, Nitrocellulose membrane filtration- based SELEX, Capillary electrophoresis – based SELEX, Cell SELEX, Microfluidic – based SELEX, Surface – Plasmon resonance, etc.

1.1.1 Affinity Chromatography and Magnetic Bead Based SELEX:-

The approach of this method depends upon the selection of aptamers which generated against target protein which is tagged with His-tag or glutathione-S- transferase (GST) and disable on beads like agarose[10]. When affinity column containing target is used immobilized bead selects the SELEX generated aptamers, still, the disadvantage of this technique this is because of untagged proteins could not be accomplished. Though, Magnetic beads are a technology by which specific aptamers can be selected without the bounding process for target protein[11].

1.1.2 Nitrocellulose Membrane Filtration Based SELEX is a method in which at least 11 rounds of SELEX selection were followed; via Nitrocellulose membrane aptamers separated [12].

1.1.3 Capillary Electrophoresis SELEX: - In conventional SELEX method about more than 15 rounds is required to form Aptamers. CE-SELEX or capillary electrophoresis SELEX is a modified SELEX method developed in 2004[13,14]. In this method from unbound sequences, the target bounded sequences are separated by electrophoresis mobility difference, which is a highly active separation method.

1.1.4 Cell- SELEX:-

Daniels et al. Firstly developed the Cell SELEX method in 2003 and against Tenascin-C a DNA aptamer was successfully obtained by using a glioblastoma-derived cell line, U251[15]. For the improvement of the success rate of aptamer screening various types of modified cell SELEX methods are established. Hicke et al developed a hybrid SELEX method in 2001 which merged the purified protein-based SELEX and advantage of Cell-SELEX[16.]

Cell SELEX utilizes a live whole cell as a target by which the possibility of selected aptamers was increased to be used for therapeutic and diagnostic use. Cell-SELEX has many advantages in comparison with in vitro SELEX like

a) We can use this method to discover unknown surface proteins or to generate new biomarkers
b) Molecular targets are in their native conformation which is present on the surface of cells
c) Before selection, there is no need for protein purification.

Because of these various types of multifunctional SELEX methods many more aptamers can be generated and selected.

1.2 The Generation of Cell-Specific Aptamers for Drug Delivery Systems:-

The target-specific cell type and a malignant cell type can increasing the number of aptamers. For most of the cell-specific aptamers generally the purified protein-based SELEX method is used and utilizing intact cell-based SELEX and purified protein-based SELEX process they can be characterized and isolated. The SELEX methods can be useful for binding specific biomolecules targets. The complexes of proteins and libraries are loaded into nitrocellulose filters. In the traditional methods, the purified proteins are generally cell restricted on an appropriate affinity sorbent (bead, resin, chip, plate). Further that are the washing process occurs with a buffer solution, the two species have found. The unbound oligonucleotides are removed from the complexes and the bound species are immediately recovered and reamplified for next selection cycle. As Cell-Specific homing agents Generation of new aptamer still poses an important task. A selection was performed by recombinant proteins because of the unavailability of the desired receptor species, physical properties, and labile native confirmations. The cell-based selection, specific cell surface molecules or membrane receptors can be directly targeted within their native environment, allowing enrichment cell-specific aptamers.

Cell-based SELEX hand over auspicious alternative for the development of aptamers which binds particularly to a specific target cell[7,18]

They are of two types:

- Positive selection with the target cells
- Counter selection with non-targeted cells.

Therefore, the specificity and affinity of aptamers essentially depend upon the differences between 2 types of cells.

2. The Development of Cell Specific Aptamers for Targetd Drug:-

Cell type-specific aptamers targeting cell surface receptors or biomarkers. They have been used for targeted drug delivery. They increase the therapeutic and reduces potential toxicities due to the cellular internalization in the target cells. The DNA and RNA aptamers have been conferred he selectivity in cell type interaction.

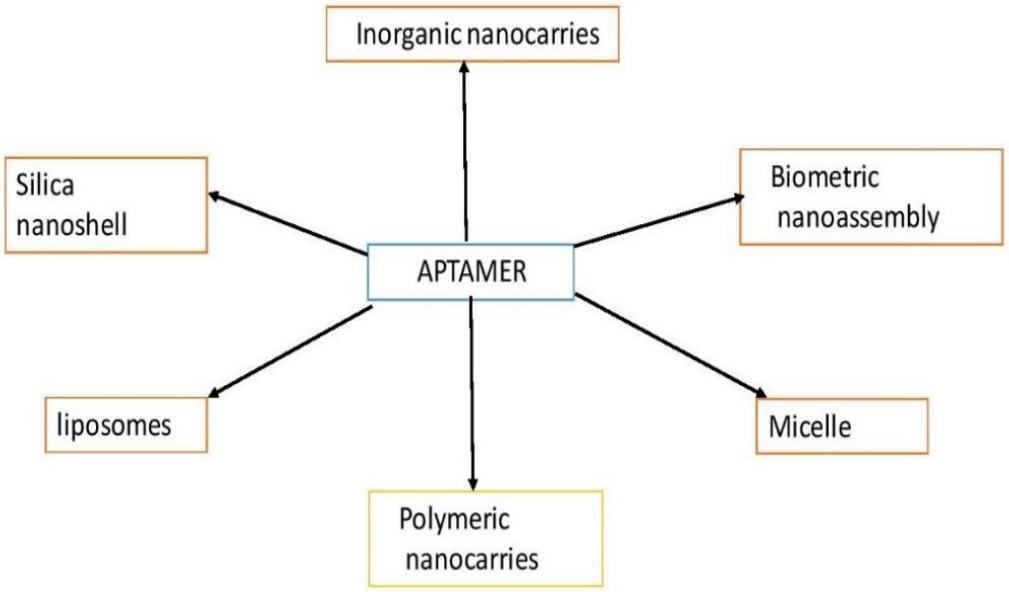

Figure: 2 An Aptamer ligand based different nanocarriers system that uses for drug delivery system with high affinity and efficacy.

Aptamers have shown a very high affinity and selectivity with respect to their targets, in comparison with antibiotics. The therapy protocols based on Aptamers are the affinity and the specificity of the nucleic acid that provide molecular recognition. Depending on the nature of the target substance the Kd values of aptamers can differ. Aptamers have Kd's between 10nM and 10pM for proteins, which are usually present in cells at a concentration between uN and Nm[19]. Small molecules are present in cells at a concentration far higher than protein concentrations. During the selection process, there is an enrichment of aptamers sequences, based on binding of their target. Aptamers shows high selectivity against their target and because of this, they bind to their targets for segregating closely related molecules from their connected molecules from their targets based on of small structural changes.

Structural data on aptamer target complexes will helpful for the rational exploration and optimization of new drug targets are important in the study of the molecular recognition process. For several aptamers in complex with their same ligand determination of three-dimensional structures are done at high resolution. At physiological pH nucleic acid is strongly negatively charged. For other polymers mainly acidic many of the aptamer's target proteins are ligands. This attends aptamer protein interactions that are dominated by electrostatic interaction. The finding that electronegative pockets within the RNA fold were responsible coordination of positively charged portion. It has also been shown that 80% of the binding

energy was contributed by hydrogen bonding. Other forces, like the stacking of aromatic rings and Van Vaals shapes, are also involved.

One example of aptamers-target complex that has been studied in detail is an RNA aptamers-Tat protein complex[20].The Kd of this complex is very low 0.1Nm sequences of the aptamer in comparison with the natural target suggested the existence of two binding sites. This was supported by the determined structure of the aptamer complex with two argininamide molecules. The major groove to make space for two argininamide molecules. Employing hydrogen bonds on the G bases, the argininamide molecules bind and there is a need for stabilized binding which is done by stacking interactions.

3. ADVANTAGES OF APTAMERS:-

The advantages of aptamers have been modifying targeted therapeutics agents. Researchers have been raising and modifying antibodies. Antibiotics can be detect specific circulating proteins and develop targeted therapeutic agents. Antibodies are highly effective and plays a vital role in various applications. They are unique aptamer advantages for targeted drug delivery systems. That can overcome some difficult scientific challenges are as follow. The advantages of aptamers are non-immunogenic, high penetration to tissue therefore cross blood-brain barriers, thermally stable, short production time, etc.

Small molecules targeted for drug delivery system :

The size of molecules as small as 60 Daltons. They are ten times smaller than the smallest antibody targets. Small molecule drugs, peptides, dyes, and viral particles have been developed wide range molecules. The different range of the molecules can be used for selective aptamers.

3.1 Non-immunogenic and non-toxic effects:-

Aptamers can be developed to selectively bind molecules that are not very immunogenic, such as small molecule drugs[21]. Whereas the production of aptamer does not involve any animal or living cells. So, it is possible to select for aptamers to toxic compounds. The compounds including zootoxins and pathogenic bacteria.

3.2 Design Stable Molecular "Sensors" and "Switches":

Aptamers undergo a conformational change upon ligand binding. They are alters binding to a second effector or changes the enzymatic activity of the aptamer. Allosteric aptamers coupled with fluorescence quenching for direct detection assays, development of biosensors, or *in vivo* imaging. Simplification of assay design and elimination of wash steps was done by direct detection. Aptamers that change conformation upon binding can be used to regulate protein expression or protein function *in vivo*, switching "On" and "Off" based on the availability of a particular ligand[22].

3.3 Penetrate Tissues and Cells:-

Aptamers are short. They are useful to reach particular targets by penetrating tissues. They penetrate the blood brain-barrier also. Without external help, some aptamers can enter cells. Some also showed apoptotic activity[23.]

3.4 Perform Simple Chemical Modifications:-

Enhance affinity, stability, or solubility through sequence-specific modifications. In biological fluids, survival time can be extended by increasing nuclease resistance by functional groups.

3.5 Generate Enzymatic Aptamers:-

Aptamers are allosteric aptamers that binds to a particular ligand further which goes through a conformational change by which upstream or downstream gene expression affected. For a growing number of ligands, Aptazymes was developed in which thiamine pyrophosphate, cyclic nucleotide monophosphates, flavin mononucleotide (FMN), adenosine triphosphate (ATP) are included [24.]

3.6 Reduce Manufacturing Time and Cost:-

Once the sequences of optimal aptamers are selected, the production of new batches of material is rapid and cheap. Aptamers including less than ~75 bases can be chemically synthesized. Production is easy to multi-gram batches.

3.7 Produce Stable Products:-

Aptamers can be stored long-term and transported at normal temperature. Denaturation of aptamers at high temperatures is a reversible process. Aptamers can re-form to their correct 3D configuration at room temperature [25] .

3.8 Improve Lot-to-Lot Reproducibility and Simplify Regulatory Procedures:-

Aptamers are chemically synthesized, simplifying scale-up. they enabling a high degree of manufacturing control from batch to batch[26]. No organisms (animals, cells) are involved in the production. So, regulatory procedures are reduced when compared to animal-based production.

4. THERAPEUTIC USES:-

Aptamers are used increasingly for the replacement option mainly for antibody. The specific features in the following

4.1 High Specificity and Efficiency –

Aptamers possess high affinities towards the selected molecule as compared to antibiotics. The nucleic acid aptamer's selection is very simple [27,28.]

4.2 Route of Administration:

Aptamers are advantages for tumour penetration and blood clearance due to low molecular weight and good solubilityTheaptamer can be administered by either intravenous or subcutaneous injection29.

4.3 Nonimmunogenic and Nontoxic:

The aptamers are non-toxic and non-immunogenicity. Thee high doses of aptamers are not toxic in rats[30.]

4.4 Optimal

5. APPLICATIONS OF APTAMERS:-

Aptamers can be selected against bacteria and viruses with different binding affinities which is important to a specific target with a particular binding affinity which gives a proper result which is an important application of aptamers. In various organisms (bacteria and viruses) specific aptamer binds with-

Table: 2 List of aptamers selected or use against viruses.

Aptamer	Backbone	Target	Type of Virus	Reference
Clone2	DNA	NS1 protein	Zika	31
Clone10	DNA	NS1 protein		
HA12-16	RNA	Glycosylated HA	Influenza A virus (H5N2)	32
HBs-A22	RNA	Surface antigen	HBV	33
RNA-Tat	RNA	TAT	HIV-1	34,35
A9	DNA	HA	Influenza A virus (H9N2)	36
B4	DNA	HA	Influenza A virus (H9N2)	37
B40	RNA	Gp120	HIV-1	38
A-1	RNA	Gp120		39
1.1RNA	RNA	RT		40
R12-2	DNA	RT		41
G6-16	RNA	NS3 protein		42
27v	DNA	NS5B		43,44
R-F t2	RNA	NS5B	HCV	45
G5	RNA	Helicase domain of NS3		46
C4	DNA	Core protein		47,48
PAN-2	DNA	Residues in the N-terminal of the PAN of the influenza A virus polymerase	Influenza A virus (H1N1, H5N1, H7N7, H7N9)	49
F2	RNA	E6 Protein	HPV 16	50,51
39SGP1A	RNA	EBOV sGP	EBOV	52,53
8- 3	RNA	HAs from H5N1 and H7N7	Influenza A virus (H5N1) and (H7N7)	54,55
S15	DNA	Envelope protein domain 3	Denv-2	56
C7	DNA	HA(101-257)	Influenza A virus(H9N2)	57
Clone B	RNA	HA	Influenza A	58
A22	DNA	HA(91-261)	virus(H3N2)	59
P30-10-16	RNA	Whole virus		60
NG8	DNA	Helicase	SARS-CoV	61

Table: 3 List of Aptamers selected or use against bacteria.

Aptamer	Backbone	Target	Type of Bacteria	Reference
Apt22	DNA	Whole bacterium	Salmonella Paratyphi A	62
C10	DNA	S.EndotoxinC1		63
R12.06	DNA	Alpha toxin		64
Antibac1	DNA	Peptidoglycan		65
SA20	DNA	Whole bacterium	S. aureus	66
PA#2/8	DNA	Protein A		67
				68
APTseb1	DNA	S.Endotoxin B		
I-2	RNA	OmpC protein		69
C4	DNA	Whole bacterium		70
SAL 26	DNA	Whole bacterium	S. typhimurium	71
ST2P	DNA	Whole bacterium		72
crn2	DNA	Whole bacterium		73
crn1	DNA	Whole bacterium	S. enteritidis	74
S25	RNA	Mix .of 10 strains of S. enteritidis		
InApt B12	DNA	Whole bacterium	E. coli K88	75
AM-6	DNA	Whole bacterium	E.coli 0158	76
A8	DNA	Internalin A	L. monocytogenes	77,78

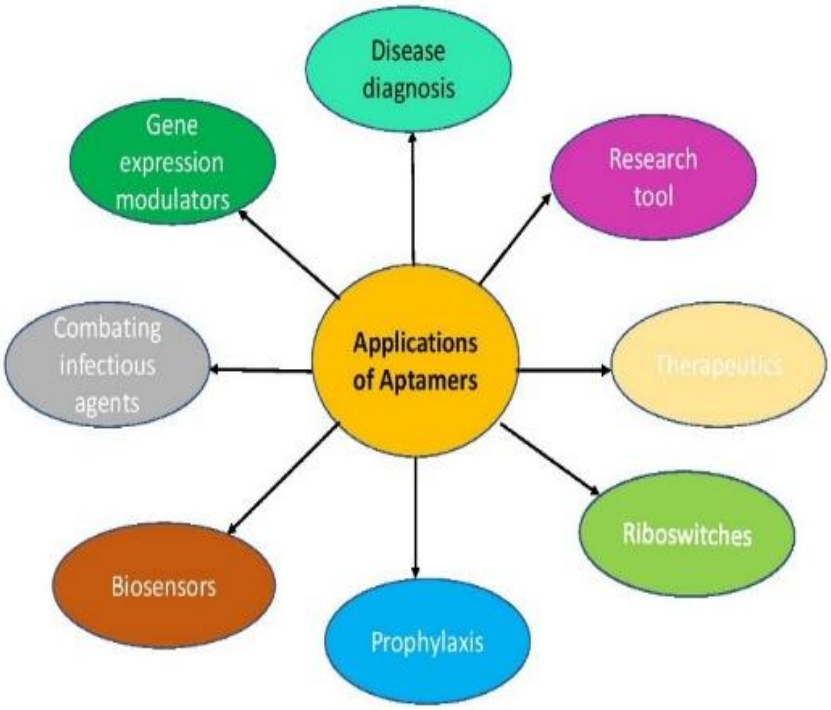

Figure: 3 Applications of Aptamers.

5.1 Aptmaers in Prophylaxis:-

The application of aptamers is not limited to target delivery. The function of aptamers in prophylactic is useful. The target drug binds to their cognate molecules[79].The molecules either be intracellular, extracellular or small molecules such as ATP. Nowadays, increased chances of associated urinary tract infection[80.]

5.2 Aptamers as Riboswitches:-

Riboswitches are naturally occurring RNA sequences with structurally recognised to modulate gene expression. The riboswitches are helpful in the cells switch their expression platforms.

5.3 Aptamers in Disease Diagnosis:-

The diagnosis of different diseases like brain diseases, cardiovascular diseases, etc .They are helpful to detect the small size molecules, stable folding, and economy. Their advancement in application of diagnosis such in diseases diagnosis, bio imaging and biomarker discovery. The biomarkers are important in treatment of cancer. In the future, aptamers would possibly eliminate the use of antibodies from the detection approach by replacement with second generation biotinylated nucleic acids or peptide aptamers[81] .The high affinity and specificity of aptamers make them ideal diagnostic agents. For a respective target they can be used for molecular recognition.

Aptamers for the identification of various pesticides in the environment have been also developed recently like fungicide carbendazim[82], acetamiprid and atrazine[83], and chlorpyriphos[84]. aptamers have been generated against various types of herbicides [85]and insecticide [86], which may cause reproductive damage in humans.

5.4 Aptamers As Biosenseros:-

For detection of environmental contaminant, interesting tool for biosensors aptamerscan be used. They also used as chip-based biosensors array by immobilizing fluorescent labelled nucleic acid aptamer on a glass slide[87.]

An examples of the recently developed biosensors include the following:

- Aptamer-based biosensors to target disease biomarkers, such as - platelet-derived growth factor , a cancer related protein, to help diagnosis of cancer development .
- Biosensors for the azole class of antifungal drugs with the application of therapeutics uses.
- Biosensors harbouring DNA aptamers targeting B-lactoglobulin for the detection of milk allergen .
- Highly sensitive biosensors for the detection of human epidermal growth factor receptor 2 with application of breast cancer cells .
- Biosensors for the detection of bisphenol A.

Different nanomaterials has been enhanced by Biosensors technique. Biosensors can be enhanced by using biomaterials[78,79].For example, antibiotics to form a "sandwich'' structure. A good example of this is – 1) The graphene-based biosensor targeting B-globulin for the detection of milk allergen and 2) The biosensor for the detection of human epidermal growth factor receptor .In the biosensor developed by Wiedman et al. for the azole class of antifungal drugs, two aptamers were combined to form a "sandwich" structure .It has been determined that the binding affinity and specificity of aptamer target complex could be increase by eliminating the non-binding domain of

aptamers by improving the density of the binding domains[88].

5.5 Aptamers As Modulator of Gene Expression:-

Chimeric RNA molecules are produced by fusion of aptamers with targeted ribozyme. They serve as molecular sensors. The nucleic acid can regulate by small molecules

5.6 Aptamers as Research Tools:-

They have wide application in research tools. Their main effect as specific inhibitors of intracellular signalling pathways. The example an inhibitory aptamer is the mitogen activated protein kinase (MAPK) RNA aptamers[89]. Inhibitory RNA aptamers used as novel anticancerous therapeutic tools

5.7 Aptamers as Molecular Mimics:-

Aptamers can be selected the simple chemistry of selection the enhancement for the utility of aptamers , composite RNA were also designed and selected for function . Another example of aptamers as molecular mimic is a spinach aptamer based on RNA mimicking green fluorescent protein[90].

6. CONCLUSION:-

We have a detailed analysis of the aptamers as target drug delivery techniques. Aptamers have a significantly wide range of applications. Most of the Aptamers designing techniques have been successfully completed because of their better advantages. The advantages of aptamers have unique characteristics. There are lots of therapeutics uses of aptamers in nanomedicine due to their small size, higher penetration in tissue, high specificity, and affinity. In the chemical modification, the variety of molecules like RNA, proteins, peptides, antibody drugs and nanoparticles are easily conjugated. Aptamers are now fatly explored for use in various other diseases like cancer, arthritis, etc. Due to less toxicity and more target specific-binding, the aptamers designing binds to their specific structure.

This review will helpful in understanding the development of all cell-specific targeted drug delivery. Aptamers have also a beneficial role in diagnostic tools due to the understanding of the efficacy of drug. Aptamers will be the future of diagnostic and therapy because of their stability, specificity, and versatility. It will also reduce the manufacturing time and cost, and improved lot-to-lot reproducibility. It will also help in the drug delivery system and pharmaceutical companies.

AUTHOR CONTRIBUTION:-

MayurSadar and SaloniKhandelwal collected data and wrote the manuscript. MayurSadar designed and edit the manuscript. Prof. Rahul Sarode and Prof.Dr. K.R. Biyani checked and revised the article. Author And Co-authors have read and approved the final manuscript.

CONFLICT OF INTERESTS:-

The authors declare that there is no conflict of interests regarding the publication of this paper.

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