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FORMULATION AND EVALUATION OF NOVEL HYDROGEL BASED DRUG DELIVERY SYSTEM FOR RESVERATROL TARGETING GLIOBLASTOMA

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ABSTRACT

This research aims to create a novel hydrogel-based delivery system for resveratrol, a natural compound with anti-cancer effects, to target glioblastoma, a highly aggressive brain cancer. The hydrogel is designed to deliver resveratrol directly to the tumor, improving its effectiveness while minimizing side effects. The study involves the formulation of the hydrogel, testing its physical and chemical properties, and evaluating its ability to release resveratrol into glioblastoma cells. The findings suggest that this delivery system has potential for enhancing the treatment of glioblastoma.

KEYWORDS: Glioblastoma, Hydrogel, Cancer Treatment, Targeted Therapy.

INTRODUCTION

Glioblastoma[1,4]

Glioblastoma is a type of brain cancer. It's the most common type of malignant brain tumor among adults, making up about half of all brain tumors in the U.S. Each year, about 12,000 people are diagnosed with glioblastoma. It's usually very aggressive, which means it can grow fast and spread quickly.

Despite a lot of research, there is no cure for glioblastoma, but there are treatments to help ease symptoms. People with glioblastoma who are not treated live an average of about 4 months. Those who do get treatment live for about 12 to 15 months.

➢ Where It Forms in the Brain

A glioblastoma is a type of astrocytoma, a cancer that forms from star-shaped cells in the brain called astrocytes. In adults, this cancer usually starts in the cerebrum, the largest part of your brain.

Glioblastoma tumors make their own blood supply, which helps them grow. It's easy for them to invade normal brain tissue.

➢ Glioblastoma Symptoms

Glioblastoma symptoms depend on where in the brain the tumor is. Because glioblastomas grow quickly, pressure on the brain usually causes the first symptoms.

The tumor can cause

- Constant headaches
- Seizures
- Nausea and vomiting
- Trouble thinking
- Drowsiness
- Memory loss
- Changes in mood or personality.

➢ The term Glioblastoma Causes and Risk Factors

Experts aren’t exactly sure what causes glioblastoma. But certain things may make you more likely to have one, such as

1. Prior radiation to the head: If you previously got radiation to treat brain tumors or cancers that may have spread to the area, it can increase your risk of having a Exposure to chemicals and other cancer causing agents may also increase your risk of genetic mutations.
2. Age and gender: It’s more common among those who are 50 or above. The average age at diagnosis is 64. Men are more likely to have it.
3. Race: It’s more common among White people than among Black, Asian, and Indigenous groups.

❖ Types of Glioblastomas

There are two types

1. Primary glioblastoma. It makes up around 90% of the cases. This type of tumor tends to be aggressive and grows fast. It's more likely to affect older people. You're also likely to have a shorter life expectancy.
2. Secondary glioblastoma. This type usually develops from a low-grade glioma – a type of tumor found in the brain or spinal cord. It's more likely to affect younger people, and it's usually in the frontal lobe of the brain. The survival rate for this type tends to be better than for primary glioblastoma.

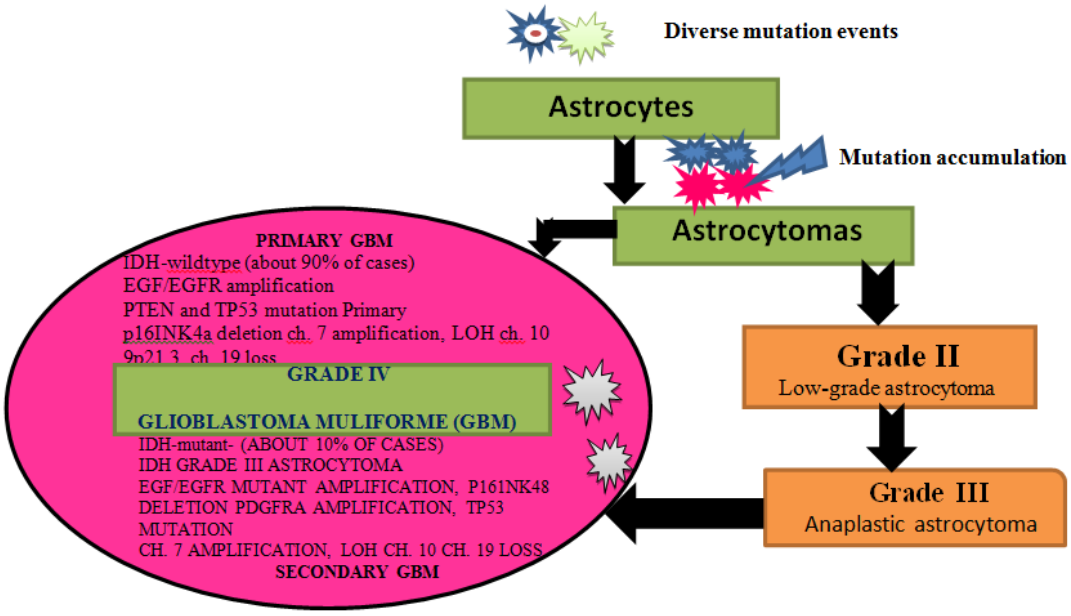

Fig. 1: Primary and Secondary Glioblastoma Multiforme origin and genetic changes.

Pathophysiology of glioblastoma[5]

Is a very aggressive brain tumor that grows quickly and is hard to treat. Here's a simpler breakdown of how it develops and affects the brain.

1) **Genetic Changes**: It often has changes in specific genes (like TP53, EGFR and PTEN) that help the tumor grow and survive
2) **Fast Growth**: Glioblastoma cells multiply quickly, forming a dense tumor that spreads into nearby brain
3) **New Blood Vessels**: The tumor creates new blood vessels to get more nutrients and oxygen, but these vessels are often messy and disorganized.

4) **Invasion**: The tumor invades surrounding brain tissue, making it hard to completely remove with surgery.
5) **Supportive Environment:** The area around the tumor, including immune cells, helps it grow and makes it harder to treat.
6) **Energy Needs**: Glioblastoma cells change how they use energy, often taking in more glucose to fuel their rapid growth.
7) **Blood Supply and Lack of Oxygen (Hypoxia):** GBM grows so fast that parts of the tumor don't get enough oxygen. To survive, the tumor sends signals to create new blood vessels. These new vessels help supply nutrients but are often abnormal and can leak, which may cause brain swelling.
8) **Disrupting the Brain's Protective Barrier**: The brain has a protective barrier called the blood-brain barrier (BBB) that keeps harmful substances out. GBM weakens this barrier, making it easier for cancer cells to spread. But this also makes delivering treatment directly to the tumor more difficult.

Glioblastoma is a very aggressive brain tumor that spreads quickly, makes it hard to treat with surgery or drugs, and leads to serious symptoms and a poor outcome.

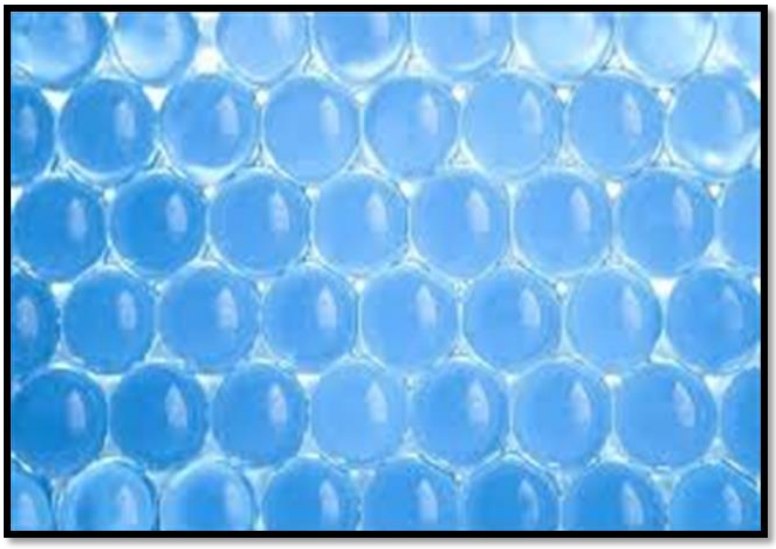

Image 1- Hydrogel.

Hydrogel[6,8]

The term "hydrogel" is derived from two parts: "hydro-", which means water, and "-gel", which refers to a semi-solid substance that can retain its shape.So, hydrogel essentially means

a gel-like material that can absorb and retain a large amount of water within its structure while maintaining its form.

Hydrogel is a network of polymer chains that are hydrophilic, meaning they can absorb and retain significant amounts of water. Despite their high water content, hydrogels maintain a distinct three-dimensional structure due to cross-linking between polymer chains, which prevents them from dissolving in water.

Key features of hydrogel[9,15]

Water Absorption: They can absorb and hold water, sometimes up to hundreds of times their dry weight.

Soft and Flexible: Hydrogels often have a jelly-like consistency, making them soft and flexible.

Hydrogels can be made from natural or synthetic materials, and their properties can be tailored for specific applications by adjusting the composition of the polymers and the degree of cross-linking.

Hydrogels are materials that can hold a lot of water and still stay solid. There are different types of hydrogels, depending on how they're made or their properties. Here are the main types in simple terms.

1. **Natural Hydrogels:** These are made from substances found in nature, like gelatin or alginate (from seaweed). They are often used in medicine because they are biocompatible, meaning the body accepts them well.
2. **Synthetic Hydrogels:** These are made in a lab using chemicals like polyacrylamide or PEG (polyethylene glycol). They can be designed to have specific properties, like being stronger or lasting longer.
3. **Physical Hydrogels:** These hold together through weaker bonds like hydrogen bonds or interactions between chains. You can think of these bonds like magnets that can come together and pull apart easily. Physical Hydrogels: These hold together through weaker bonds like hydrogen bonds or interactions between chains. You can think of these bonds like magnets that can come together and pull apart easily.
4. **Chemical Hydrogels:** These are held together by strong chemical bonds Glioblastoma uses many receptors to grow and spread. Targeting these receptors is difficult, but

research is ongoing to develop better treatments that can block these signals and control the disease more effectively. Glioblastoma uses many receptors to grow and spread. Targeting these receptors is difficult, but research is ongoing to develop better treatments that can block these signals and control the disease more effectively. (called covalent bonds). This makes them more stable and less likely to break apart. Chemical Hydrogels: These are held together by strong chemical bonds (called covalent bonds). This makes them more stable and less likely to break apart.

5. **Responsive Hydrogels:** These change their shape or behavior when something in their environment changes, like temperature, pH, or light. For example, some hydrogels can swell or shrink depending on the temperature around them.
6. **Hybrid Hydrogels:** These are a mix of natural and synthetic materials to get the best of both worlds. They are designed to have good strength while being biocompatible.

These hydrogels are used in many areas like drug delivery, wound care, and tissue engineering.

Application[16]

- **Medical and Biomedical:** Used in wound dressings, drug delivery systems, contact lenses, and tissue engineering. Medical and Biomedical: Used in wound dressings, drug delivery systems, contact lenses, and tissue engineering.

- **Agriculture:** Utilized in soil conditioning and water retention in agriculture. Agriculture: Utilized in soil conditioning and water retention in agriculture.

- **Consumer Products:** Found in products like diapers and sanitary pads due to their absorbent properties. Consumer Products: Found in products like diapers and sanitary pads due to their absorbent properties.

The formulation of hydrogels for brain cancer is necessary to address the shortcomings of current treatment methods, improve the targeting and efficacy of therapies, reduce systemic toxicity, and ultimately provide a more effective and patient-friendly approach to combating this challenging disease.

Advantages of hydrogel[17,19]

1. Hold lots of water.
2. Safe for the body.

3. Slow and steady medicine release.
4. Soft and flexible.
5. Less painfull.
6. Adhesion to tissues.
7. Non toxic degradation.
8. Ability to carry large molecules.

Disadvatages of hydrogel[20,21]

1. Weak mechanical strength.
2. Limited drug load capacity.
3. Difficult sterilization.
4. Slow response time.
5. Biodegradation issue.
6. Complex manufacturing.

Resveratrol[22,24]

Resveratrol is a natural compound found in the skin of grapes, berries, and some other plants. It is known for its antioxidant and anti-inflammatory properties, which means it helps protect cells from damage and reduces inflammation. Resveratrol is popular because it's believed to have health benefits like improving heart health, protecting the brain, and even helping to fight cancer. It's also found in red wine, which is why some people associate wine with health benefits. However, it's available in supplements and extracts as well. Resveratrol is a natural compound found in the skin of grapes, berries, and some other plants. It is known for its antioxidant and anti-inflammatory properties, which means it helps protect cells from damage and reduces inflammation. Resveratrol is popular because it's believed to have health benefits like improving heart health, protecting the brain, and even helping to fight cancer. It's also found in red wine, which is why some people associate wine with health benefits. However, it's available in supplements and extracts as well.

Resveratrol exists in two main forms: cis-resveratrol and trans-resveratrol. Here's a brief and easy explanation: Resveratrol exists in two main forms: cis-resveratrol and trans-resveratrol. brief and easy explanation.

- **Trans-Resveratrol:** This is the more common and stable form of resveratrol. It is the one most often found in grapes, red wine, and supplements. Trans-resveratrol is considered

the most active and beneficial form because it has stronger antioxidant and anti-inflammatory properties

- **Cis-Resveratrol:** This form is less stable and less common than trans-resveratrol. It can form when trans-resveratrol is exposed to light or heat. While it also has some health benefits, it's less potent than trans-resveratrol.

Both forms can offer health benefits, but trans-resveratrol is the one most widely studied and used in health products due to its stability and effectiveness.

Mechanism of action of resveratrol on brain cancer[25,26]

Resveratrol uptake

↓

Pathway modulation

Inhibit NF-Kb and IP3K/AKT pathways

Activates p53 and AMPK

↓

Anti-proliferation

Induce cell cycle arrest

↓

Apoptosis induction

Activates mitochondrial apoptotic pathways and caspases

↓

Inhibition of angiogenesis & metastasis

Reduces VEGF and MMPs, decreasing tumor growth &invasion

↓

Tumor suppression

Reduces cell proliferation, angiogenesis & metastasis, leading to cancer cell death

MATERIAL AND METHODOLOGY

MATERIAL

Grape seeds: Collected from Local area market of Shrirampur, in the February.

Chemicals

PEG, Ferric Chloride, Lead Acetate, Sodium nitrite, Sulfuric Acid, Sodium Hydroxide, Nitric Acid, Bromine water, Millons Reagent, Potassium Dichromate.

Equipments

Beaker, Heating Mental, Test tubrs, Conical flask, Water bath, whatman Filter paper, Measuring cylinder, Test tube stand ,Stirrer, Storage vials.

METHODOLOGY

Extraction of resveratrol[27,29]

Extraction of Grape Seed Powder Using Propylene Glycol

Grape seed extract is widely studied for its antioxidant and therapeutic properties, especially for applications like drug delivery and cancer treatment. Using propylene glycol as a solvent offers advantages such as better solubility of polyphenols, biocompatibility, and potential use in pharmaceutical and cosmetic formulations.

Materials and Equipment

- Grape seed powder (dried and finely ground)
- Propylene glycol
- Distilled water (if preparing a mixed solvent system)
- Water bath (temperature control)
- Filter paper
- Storage vials (amber-colored for light protection)

Procedure

1. Preparation of Grape Seed Powder

Obtain dried grape seeds.

Grind them into a fine powder using a grinder or milling machine.

Sieving can help obtain uniform particle size for efficient extraction.

2. Selection of Solvent System

Pure propylene glycol: Suitable for direct formulation in pharmaceutical and cosmetic products.

3. Extraction Process

Maceration Method (Simple Extraction)

1. Weigh 10 g of grape seed powder.
2. Add 100 mL of Propylene glycol in a grape seeds powder
3. Stir continuously at room temperature (25–30°C) for 24–48 hours in a dark environment.

4. Filter the extract using Whatman filter paper
5. Collect the supernatant and store in amber vials.

Image 3: Extraction of grape seeds.

Extraction value = (Weight of extract obtained/weight of crude material used)×100

Weight of grape seeds powder =50g

Weight of dried extract after solvent evaporation =17.28g

Extraction value=17.28/50×100=34.56%.

RESULT AND DISCUSSION

The result of the preliminary phytochemical examination of phenolic extract of grape seeds are given below.

Table 4: Observation table of identification test.

Plant constituent	Test performed	Obeservation	Result
Phenol	Ferric choride test	Blue, green red or violet color	+
	Lead acetate test	Formation of white ppt	+
	Libbermanns test	Blue, green or red color after adding NaOH	+
	Bromine water test	White ppt formation	+
	Millons test	Red coloration upon heating	+
	Dichromare test	Brown or green coloration	+

Physicochemical assessment of formulated hydrogel

1. Physical Appearance

Table 5: Physical properties of hydrogel.

Sr. no	Specification	Observation
1	State	Semi-Solid
2	Colour	Pale yellow
3	Odour	Odourless
4	Texture	Smooth

2) pH

The pH of an injectable hydrogel typically ranges from 6.8 to 7.4, making it close to physiological pH to ensure biocompatibility and minimize tissue irritation.

Table 6: Determination of pH.

Sr. no	Formulation	pH
1	F1	6
2	F2	7
3	F3	6
4	F4	6
5	F5	6

3) Spreadability

The spreadability of an injectable hydrogel refers to its ability to flow or spread when applied, which affects its ease of injection and uniform distribution at the target site. This property is typically assessed to ensure smooth administration and effective therapeutic delivery.

Table 7: Determination of spreadiability.

Sr. no	Formulations	Spreadability
1	F1	29.2sec
2	F2	26.5sec
3	F3	31sec
4	F4	28sec
5	F5	27.4sec

Table 8: observation table of evaluation test of hydrogel.

Sr.no	Parameters	Observations
1	Colour	Pale yellow
2	Odour	Odourless
3	P^H	7
4	Consistency	Semi-solid
5	Spreadiability	25sec

DISCUSSION

This study focused on developing a hydrogel-based system to deliver resveratrol directly to glioblastoma (GBM) tumors. Resveratrol is a natural compound with anti-cancer effects, but it has poor water solubility and gets cleared quickly from the body. To solve this, we used a gelatin-based hydrogel that can be injected and forms a gel at body temperature.

The hydrogel showed good physical properties like easy injection, proper gelation, and stability. It also had high drug-loading ability and released resveratrol slowly over time, which can help maintain effective drug levels at the tumor site.

Biodegradation and swelling studies showed that the hydrogel breaks down slowly and absorbs water well, which supports its use in the body. In cell studies, the hydrogel was safe by itself and showed good anti-cancer activity when loaded with resveratrol.

Overall, this hydrogel system could improve the delivery of resveratrol to brain tumors and make treatment more effective. Future animal studies are needed to confirm these results.

CONCLUSION

The novel hydrogel-based delivery system developed for resveratrol targeting glioblastoma shows promise in enhancing drug stability, controlling release, and improving bioavailability in brain tumor treatment. This formulation provides sustained release and potentially increases resveratrol's therapeutic efficacy against glioblastoma by facilitating targeted delivery to the tumor site. The system demonstrated favorable biocompatibility, stability, and preliminary in vitro/in vivo efficacy, suggesting that it could be a viable approach for glioblastoma treatment. Further studies are needed to optimize and validate its performance in clinical settings.

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