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A Review on Novel Hydrogel: Based 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.

I. INTRODUCTION-[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

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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.

Hydrogel-[5-7]

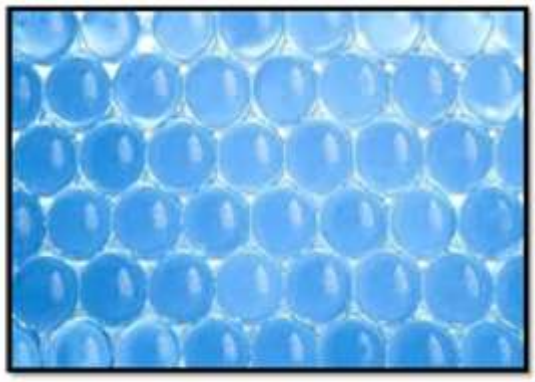

Fig01:.hydrogel

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.

Types Of Hydrogel:[8-14]

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.

RESVIRATROL[15-17]

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.

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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. Here's a 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.

Mechanism Of Resveratrol:[18-19]

- **Antioxidant:** It helps neutralize harmful molecules called free radicals, protecting cells from damage.
- **Anti-inflammatory:** It reduces inflammation, which can slow down the growth of cancer
- **Cell death:** Resveratrol can make cancer cells self-destruct, preventing them from spreading.
- **Blocks blood supply to tumors:** It stops tumors from making new blood vessels, cutting off their food and oxygen.
- **Gene regulation:** It influences certain proteins and genes that control cell survival and growth, like SIRT1 and p53.

Fig02:Grape Seeds

Synonyms[20]-Vitis vinifera seeds,grape kernel,grape pip

Biological source[21]-It is widely cultivated for its fruit(grapes),from which grape seeds are obtained as a byproduct.It is belonging to family vitaceae.

Table1.Common names-[22]

English name	Grape kernels
Sanskrit name	Draksha bija
Hindi name	Angoor ke beej
Bengali name	Angurer beej

Geographical distribution-

1. Grape seeds are found in many parts of the world, especially where grapes are grown. Some of the main regions include:
2. **Europe:** France, Italy, and Spain.
3. **North America:** The United States (mainly California) and Mexico.
4. **South America:** Argentina and Chile.
5. **Asia:** China, India, and Turkey.
6. **Africa:** South Africa

Cultivation-

1. **Planting:** Grapes are planted in good soil with lots of sunlight
2. **Watering:** They need regular water but not too much
3. **Care:** Farmers trim the vines to help them grow well and check for bugs or diseases.
4. **Harvesting:** Grapes are picked when they are ripe, usually in late summer or fall.
5. **Seeds:** The seeds are collected as a byproduct when grapes are processed.
6. So, grape seeds come from the process of growing grapes!

Botony-

1. **Shape and Size:** Grape seeds are small, oval-shaped, and usually 2-5 mm long, depending on the grape type.
2. **Outer Coat:** They have a tough outer shell that protects the seed.
3. **Seed Coat Layers:** There are several layers in the seed coat, which help keep the seed safe and retain moisture.
4. **Endosperm:** The inside part of the seed that stores nutrients for the growing plant
5. **Embryo:** The tiny part inside the seed that will grow into a new grapevine when the seed sprouts.

Chemical constituents[23]

Grapes contain a variety of chemical compounds that contribute to their flavor, nutritional value, and

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health benefits. Here are some key chemicals found in grapes:

1. **Sugars**
a. Glucose: A simple sugar that provides sweetness.
2. **Organic Acids**
a. Tartaric Acid: The primary acid in grapes, contributing to their tart flavor and stability in wine.
b. Malic Acid: Adds to the tartness and complexity of flavor.
3. **Phenolic Compounds**
a. Flavonoids: A group of antioxidants that include quercetin and anthocyanins, which give color to red grapes.
b. Resveratrol: A polyphenol associated with heart health and found mainly in the skins of red grapes.

4. **Vitamins**
a. Vitamin C (Ascorbic Acid): An antioxidant that supports immune function and skin health.
b. Vitamin K: Important for blood clotting and bone health.
c. B Vitamins: Including B6 (pyridoxine) and riboflavin, which are essential for energy metabolism.
5. **Minerals**
a. Potassium: Helps regulate blood pressure and fluid balance.
b. Calcium: Important for bone health.
c. Magnesium: Plays a role in many biochemical reactions in the body.

6.Aroma Compounds
a. Terpenes: Contribute to the fragrance and flavor profile of grapes and wines
b. Esters: Volatile compounds that add fruity aromas to grapes.

Grapes are rich in sugars, organic acids, phenolic compounds, vitamins, minerals, dietary fiber, and aromatic compounds, all of which contribute to their nutritional profile and flavor. These chemicals play important roles in human health, particularly due to their antioxidant properties

Extraction of resveratrol:[24-27]

Hot Water Extraction of Resveratrol: Detailed Procedure

Resveratrol, a potent polyphenol, is commonly extracted from sources like grapes, peanuts, and other plants. Hot water extraction is a simple, eco-friendly method to obtain resveratrol. Here's the detailed procedure:

1. **Selection of Plant Material**

Source: Choose resveratrol-rich sources, such as red grape skins or Japanese knotweed.
Preparation: Clean the material to remove contaminants. Dry it in an oven at 40-50°C or air dry in the shade until all moisture is removed.
Grinding: Once dried, grind the plant material into a fine powder using a grinder. This increases the surface area and facilitates the extraction process.

2. **Hot Water Extraction**

Weighing: Measure a known amount of powdered material (e.g., 20 grams).
Water Addition: Add the material to a flask or container with a known volume of water (e.g., 200 mL). The water should be preheated to around 80-90°C.
Heating: Maintain the temperature of the water at 80-90°C during the extraction process. This ensures effective solubilization of resveratrol.
Stirring: Stir continuously or intermittently during extraction to improve the interaction between the plant powder and water.
Extraction Time: The extraction process should last for 30-60 minutes. Prolonged heating may degrade resveratrol, so it's important to avoid overly long extraction times.

3. **Cooling and Filtration**

Cooling: Allow the mixture to cool to room temperature once the extraction time is complete.
Filtration: Use a filter (e.g., Whatman filter paper or a Buchner funnel) to separate the plant material from the liquid extract.

4. **Collection:** Collect the filtrate, which now contains the resveratrol in solution.
5. **Storage and Further Use**

Storage: The concentrated resveratrol extract can be stored in airtight containers in a cool, dark place, or refrigerated for further use.
Use: The resveratrol extract can now be used for incorporation into formulations, such as hydrogels, for pharmaceutical or research purposes.

Key Notes:
Yield Optimization: The efficiency of resveratrol extraction can be optimized by varying temperature, time, and water-to-material ratio.
Stability: Resveratrol is sensitive to high temperatures for prolonged periods, so it's important to balance extraction time and temperature to maximize yield without degradation.
This method provides a straightforward and safe way to extract resveratrol from plant materials

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using water as the solvent, suitable for preparing resveratrol for various applications like drug delivery or therapeutic formulations.

Preparation of hydrogel:[28-31]

Preparation of Hydrogel Incorporating Resveratrol

Hydrogels are hydrophilic polymer networks capable of retaining large amounts of water. Incorporating bioactive compounds like resveratrol into a hydrogel provides a sustained-release system for drug delivery. Here's how to prepare a hydrogel with resveratrol:

Brief Overview:

1. **Polymer Selection:** Choose a natural or synthetic polymer (e.g., chitosan, alginate, polyvinyl alcohol).
2. **Dissolve Polymer:** Dissolve the polymer in distilled water to create a gel-forming solution.
3. **Incorporate Resveratrol:** Mix resveratrol into the polymer solution.
4. **Cross-Linking:** Induce gel formation by adding a cross-linking agent (e.g., calcium chloride) or adjusting environmental conditions (e.g., pH, temperature).
5. **Curing:** Let the hydrogel set and stabilize.
6. **Characterization:** Analyze the hydrogel's mechanical properties, drug release profile, and biocompatibility.

Detailed Procedure:

1. Materials Needed

Polymers: Natural (e.g., chitosan, gelatin, alginate) or synthetic (e.g., polyvinyl alcohol [PVA], polyethylene glycol [PEG]).

Resveratrol: Active drug compound.

Cross-Linking Agent: Calcium chloride ($CaCl_2$), glutaraldehyde, or another suitable agent for chemical cross-linking.

Solvents: Distilled water, ethanol (if resveratrol is poorly water-soluble).

Buffers: For pH adjustment (if needed for the polymer).

2. Step-by-Step Hydrogel Preparation:

A). Prepare the Polymer Solution

1. Weigh the polymer: Select a polymer concentration (e.g., 1-5% w/v) based on the desired hydrogel properties.

2. Dissolve the polymer:

If using natural polymers like chitosan or alginate, dissolve in an aqueous solution (e.g., acetic acid for chitosan).

3. Cool: Allow the solution to cool to room temperature (if applicable).

B). Incorporate Resveratrol

1. Dissolve Resveratrol:

Resveratrol is poorly soluble in water, so you may need to dissolve it in a small amount of ethanol or DMSO.

Alternatively, prepare a fine resveratrol suspension in water by stirring or sonication.

2. Mix into the Polymer Solution:

Add the resveratrol solution or suspension into the prepared polymer solution under continuous stirring.

Ensure uniform dispersion of resveratrol within the polymer matrix.

C). Cross-Linking to Form Hydrogel

1. Cross-Linking Methods:

Chemical Cross-Linking: For polymers like alginate or gelatin:

Add a cross-linking agent (e.g., $CaCl_2$ for alginate) dropwise with gentle stirring.

For chitosan, glutaraldehyde can be used for cross-linking.

pH Adjustment: For polymers sensitive to pH, adjust the pH (e.g., neutralizing chitosan with NaOH) to induce gelation.

2. Gelation Time: Depending on the polymer and cross-linker, gelation can take from a few minutes to several hours. Leave the mixture to set until a stable hydrogel is formed.

D). Curing and Stabilization

1. Rinse and Cure: If a cross-linking agent was used, the formed hydrogel can be rinsed with water or buffer to remove excess agents.

2. Freeze or Dry: Depending on the intended application, you can freeze-dry the hydrogel to enhance its mechanical stability or retain it as a hydrated gel for drug release studies.

This method will yield a hydrogel capable of controlled or sustained release of resveratrol, making it ideal for targeted drug delivery, including cancer therapy.

II. 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

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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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