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Flavonoid-Based Smart Drug Delivery Systems in Cancer Therapy: New Hope for Precision Medicine

Yasir Anwar

Department of Biological sciences, Faculty of science, King Abdulaziz University, Jeddah Saudi Arabia

Abstract. Flavonoids are polyphenolic compounds that have powerful anticancer properties. Despite this, they are not suitable for treating cancer due to low solubility, instability, and bioavailability. To enhance their durability and bioavailability, it has been suggested that using delivery methods that include flavonoids to enhance their bioavailability may be a promising solution. Our review will focus on promising flavonoid delivery systems for anti-cancer drugs, particularly targeting cervical cancer treatments. In addition to flavonoids' enormous therapeutic potential, delivery methods are critical to achieving positive results in cancer therapy. In addition to their anticancer properties, flavonoids are also polyphenolic compounds that occur naturally. However, these compounds are not suitable for treating cancer due to their insolubility, stability, and bioavailability. By adding flavonoids to delivery systems, the properties of flavonoids can be enhanced, resulting in higher bioavailability and durability. Data obtained highlights flavonoids' great therapeutic potential as well as the importance of constructing good delivery mechanisms for cancer patients to achieve good outcomes. In conclusion, flavonoids may provide more efficient and individualized cancer treatment when incorporated into delivery systems. The adoption of flavonoid-based cervical cancer treatment methods could significantly improve the quality of life of millions of women. By encapsulating flavonoids in delivery systems, chemotherapy's adverse effects can be reduced, and patient outcomes may improve.

Keywords: Flavonoids, anticancer, nanoparticles, Drug delivery.

1. Introduction

Based on the data that is maintained by the Global Cancer Observatory (GLOBOCAN), cancer is presently considered to be one of the leading causes of death throughout the world. There is a prediction that by 2020, there will have been more than 10 million deaths as a result of illness. There is an aberrant pattern of cell growth that is characterized by the patient not being able to control the growth. Cells that produce these abnormal growths are usually caused by a substance that appears as an initiating agent and causes anomalies in the cellular machinery or mutations in the cellular DNA as a result. Often, these anomalies are found in the body after cancer has been diagnosed, in which case this cancer may spread to other parts of the body.

According to the World Health Organization (WHO), cervical cancer is one of the most prevalent forms of cancer among women worldwide, with a prevalence rate of 6.5% [1]. Breast cancer is the most frequent cancer and the second leading cause of cancer-related mortality in women globally. In less developed nations, it accounts for 21.1% and 22.1% of cancer-related deaths, second only to another common disease. Concerning cervical cancer, approximately 79 to 100 percent of cases are attributed to the human papillomavirus (HPV), which causes about

90 percent of cervical cancer worldwide. Of these cases, around 70 percent are linked to the high-risk HPV subtypes HPV-16 and HPV [1,2].

According to the HPV genome sequence, there are eight genes encoded by the virus genome, which may be classified into two categories based on the stage of infection at which they are produced [3]. Several genes, such as E1, E2, E4, E5, E6, and E7, are in the early regions of the genome [4]. Several of these genes play an important role in the processes of replication, control of transcription, and oncogenesis, as well as their expression. Amongst the genes encoded in this region are both the L1 and L2 genes, which are crucial to produce the capsid of HIV, which constitutes an envelope around the viral genome [4]. This late region also contains the genes that encode the amino acids of the NS5 protein.

The expression of the E1 and E2 proteins in the undifferentiated epithelial cells of the basal layer that have been infected by HPV begins to take place after the infection with HPV has taken place in these cells. A number of proteins are required for the replication of a virus as well as the expression of other viral proteins that are produced early in the viral life cycle [5]. It is important to note at this point that because the viral DNA can reproduce only when the DNA of the infected cells exists in duplicate, the viral replication cycle is entirely dependent upon the differentiation cycle of the infected cells at this point [4]. It has been observed that as soon as the basal cells infected with E6 and E7 begin to differentiate, two viral proteins that are known as E6 and E7 will start to be produced. Cell proliferation is stimulated by these proteins, the cell cycle is prolonged, and apoptosis is inhibited by these proteins. There is evidence that oncoproteins E6 and E7 have a direct inhibitory effect on the tumor suppressor proteins p53 and pRb through their direct interactions [2]. The E6 oncoprotein inhibits the production of apoptosis in infected cells during the course of the infection, by inhibiting the degradation of the p53 protein, which is caused by ubiquitin in the proteosomes [5,6]. It is the buildup of DNA damage that causes the development of cervical lesions and the spread of chronic infections. These lesions are caused by the activity of the oncoproteins E6 and E7 causing DNA damage to be caused by the cells. In addition, the cells that have differentiated the most in the epidermis are also those that release the virus during the death of the keratinocytes that occupy a more superficial position [5]. It is therefore possible that HPV infection can be spread from one person to another through dermal contact. In fact, micro-cuts in the basal layer of the epithelium contribute to carcinoma in situ and neoplasms. These tumors can lead to cervical cancer in the future. The figure below depicts this process. (Fig. 1).

It is common to find cervical cancer and other infections that don't go away in countries that lack adequate healthcare and do not allow the vaccination of women against HPV. It is because of this that the death rate in these developing countries is higher than those in industrialized countries where vaccines are widely available [1,2]. The research and development of new treatments for patients whose cancer was caused by HPV is of significant interest since it will result in better outcomes for those patients. In recent years, there has been a growing interest in the exploration of various methods for combating diseases and improving human health. One area of study that has gained significant attention is the use of therapeutic DNA or RNA vaccines. These innovative vaccines utilize genetic material to stimulate an immune response and provide protection against specific diseases. Researchers have been investigating the potential of these vaccines to revolutionize the field of medicine and provide a more

effective and targeted approach to prevent and treat diseases [6]. Natural substances with low toxicity, high cancer-fighting properties, and affordable costs are being used to treat different types of cancer, such as cervical cancer. Among these, flavonoids have been extensively researched. In vitro experiments have demonstrated that flavonoids can reduce viability by blocking the oncoprotein E6, leading to increased p53 activity and triggering programmed cell death [7,8].

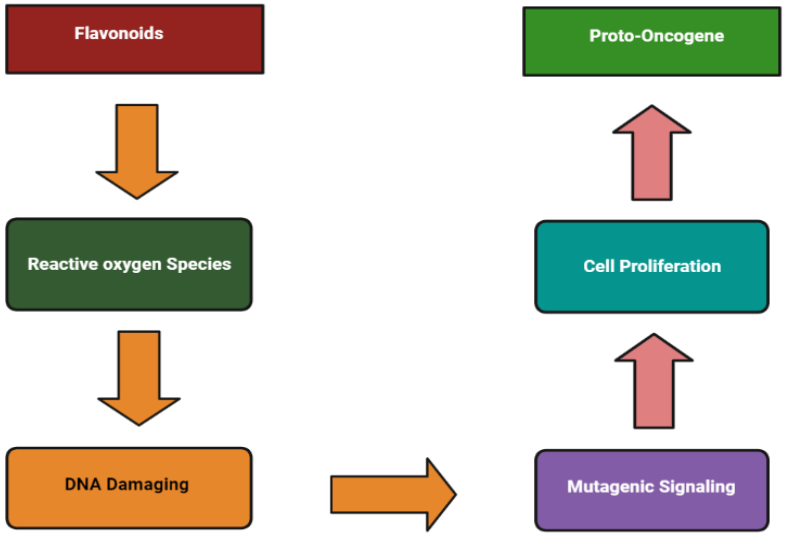

Fig. 1. Depicts a schematic diagram exerting a pathway of how flavonoids have anticancer properties.

2. Flavonoids

The C6-C3-C6 carbon skeleton base is characteristic of flavonoids, which are phenolic chemicals that may be found in plants. They are a common component of the human diet and have been demonstrated to offer numerous health benefits, including anti-diabetic, anti-oxidative, anti-inflammatory, antimicrobial, antiviral, and cancer-fighting properties [9-12]. Utilizing flavonoids as an anticancer therapy is now the primary focus of research. A number of flavonoid molecules, including epigallocatechin-3-gallate, quercetin, genistein, luteolin, apigenin, silibinin, naringenin, and kaempferol, have been found as potential anticancer agents. These flavonoids have shown significant anticancer activity through a number of different mechanisms, including the inactivation of carcinogens, anti-angiogenic effects, antioxidant effects, apoptotic effects, reduced cellular oxidative stress, reduced cell proliferation, and improved DNA repair pathways are all induced [13]. Provides a synopsis of all of these methods.

Flavonoids have been found to have anticancer mechanisms, although the paths that each mechanism takes are not yet completely known as shown in Fig. 2. Therefore, ongoing research strives to fully understand these systems to enhance their effectiveness and minimize their limitations. It is believed that two essential mechanisms of activity discovered in most flavonoids are the reduced form of responsive oxygen species (ROS) and prompting of caspase-mediated cell death through decease receptors. One of the key modes of action of flavonoids is their capacity to diminish reactive oxygen species (ROS), which in turn inhibits cell proliferation and, as a result, reduces the formation of tumors. ROS is to blame for the

irreparable damage to DNA that ultimately results in the formation of cancer cells and the uncontrolled expansion of those cells. In addition, ROS is responsible for the formation of proto-oncogenes, which are proteins that may encourage the development of additional cells. Flavonoids inhibit cell proliferation and the activity of proto-oncogenes by scavenging reactive oxygen species (ROS), which in turn lowers the probability that cancer may develop into a more advanced stage [14,15].

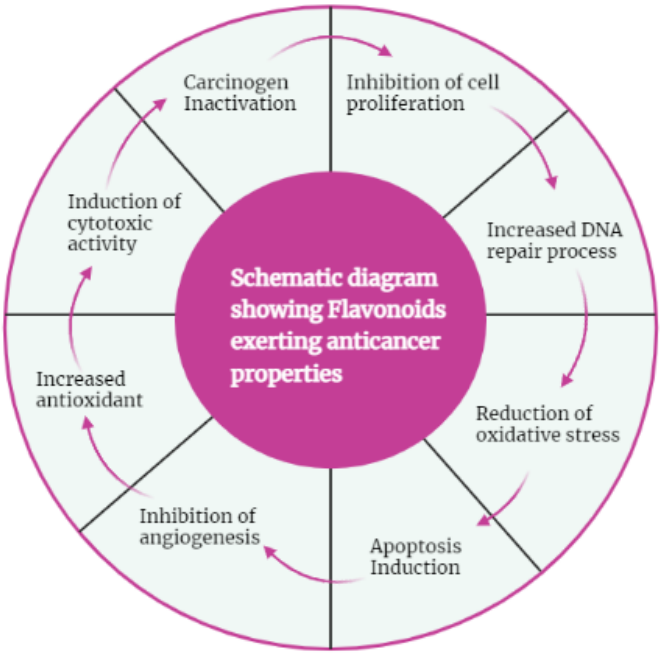

Fig. 2. Depicts a schematic diagram presenting anticancer properties of flavonoids.

Flavonoids can activate death receptors, which eventually leads to the activation of caspase 8 and the Bid proapoptotic component, which finally results in the release of cytochrome c and the induction of apoptosis [14]. Flavonoids can activate death receptors. Therefore, regardless of the particular mechanism that is involved, flavonoids induce apoptosis, which ultimately leads to the decrease of tumour size. However, the exact methods of action might change depending on the kind of flavonoid, including variations in antioxidant strength, the capacity to diminish responsive oxygen species, and the activation of programmed cell death, among other aspects [16]. To understand the distinctions in the mechanisms of action that different flavonoids have, as well as how they might be improved to increase their anticancer benefits, further research is required.

Flavonoids have been shown to have an additional mode of action in cervical malignancy, which is the reticence of tumor E6. This results in a rise in p53 levels, which then leads to the induction of apoptosis [8]. This process is exclusive to flavonoids, which increases the efficacy of flavonoids in treating cervical cancer in comparison to the efficacy of flavonoids treating other forms of cancer.

In addition, adjuvant therapy, in which flavonoids are used in combination with chemo, drugs for instance doxorubicin or paclitaxel has been the specialty of an enormous body of research. The enhanced intracellular accumulation of medications due to flavonoids in tumor cells results in a marked decrease in cell proliferation and growth. They also lower toxicity in healthy cells, so minimizing the impact of any adverse reactions. One of the fundamental drawbacks of chemotherapy may be circumvented by combining flavonoids with anticancer medications, which also has the added benefit of enhancing the anticancer action of the drug at lower doses [17–19].

2.1 Flavonoids' Mechanism of Action in Inducing Apoptosis

Regulation of Signaling Pathways: Flavonoids interact with various signaling pathways within cancer cells. For instance: They inhibit the activity of anti-apoptotic proteins (such as Bcl-2 and Bcl-xL) and promote pro-apoptotic proteins (like Bax and Bak). Flavonoids can activate caspases (enzymes responsible for apoptosis execution), leading to cell death. Some flavonoids interfere with growth factor receptors, hindering cancer cell survival signals. Flavonoids can halt the cell cycle at specific checkpoints, preventing uncontrolled cell division. This arrest provides an opportunity for apoptosis to occur. The mechanism of action inducing apoptosis using flavonoids is shown in Fig. 3.

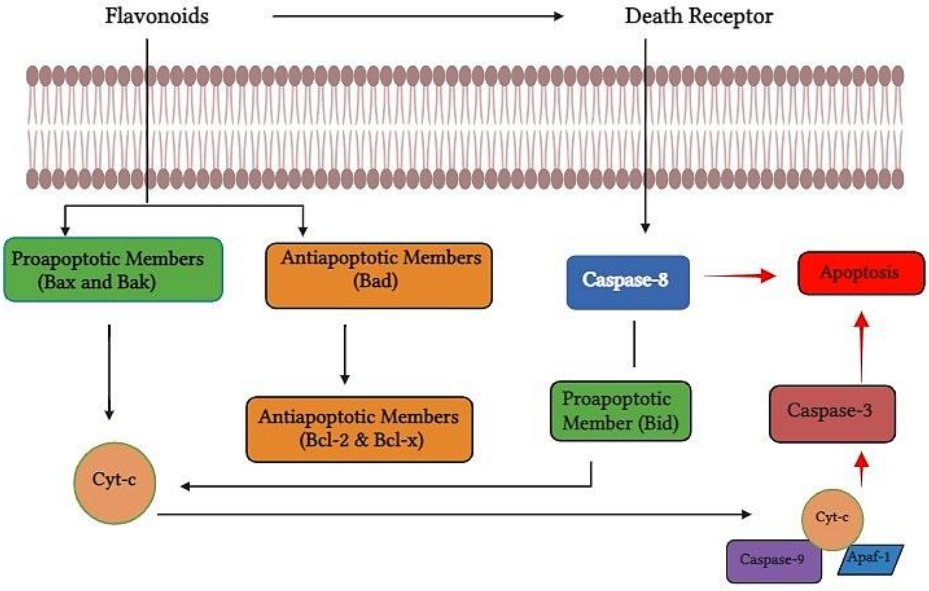

Fig. 3. Flavonoids' Mechanism of Action in Inducing Apoptosis in Cancer Cells.

2.2 Flavonoids Subclasses

Based on their biosynthetic origin, degree of oxidation, saturation, binding site and class of polyphenols known as flavonoids may be further classified into subgroups [20]. Flavonoids are also categorized according to the aromatic ring binding site. Now, flavonoids are capable of being separated into a few different subgroups.

2.2.1 Flavones

Subgroups within the family of polyphenols known as flavonoids may be identified by their degree of oxidation, saturation, binding site of the carbons between the rings C15. In human beings, flavones are associated with a variety of positive health effects. By blocking the xanthine oxidase enzyme, for instance, they are able to bring about a reduction in the formation of reactive oxygen species (ROS). This action causes the efflux pumps to become inhibited, which ultimately results in the activation of apoptosis. Flavones are also able to interact with estrogen receptors, which stops estrogen receptors from changing their shape and connecting to cancer-causing co-activators [16,20].

2.2.2 Flavonols

Flavonols are a subgroup of flavonoids with an increased corrosion state than flavones. The ground frame of flavonols contains a hydroxyl group (-OH) on carbon number 2. The most abundant sources of flavonols in nature are fruits and vegetables such as onions, apples, broccoli & beverages such as red wine, green & black tea. Quercetin is the most important flavonol and the greatest extensively studied compound in this subgroup, although Other flavonols are of scientific importance, including compounds such tamarixetin, fisetin, kaempferol, rutin, myricetin, morin, as well as rutin [20].

Within plants, flavonols are involved in plant growth, development, and defense against insects and UV radiation. In human health, flavonols have been associated with antioxidant, antibacterial, antioxidant, anti-inflammatory, and cancer-fighting properties. Quercetin has been extensively studied for its potential anticancer effects. Matrix metalloproteinase (MMP) inhibition limits cancer cell proliferation and metastasis and promotes programmed cell death of tumor cells. Additionally, quercetin prevents oxidative stress, inhibits angiogenesis, & interrupts cell cycle progression through epigenetic changes [7,15,22].

2.2.3 Flavanones

A category of flavonoids known as flavanones are distinguished by the presence of saturated and deoxygenated carbons at positions 1 and 2 in the base structure of their molecule. Flavonoids, found in the skin of fruits and flowers, give plants their bright colors and help attract pollinators, repel pests, and shield against UV rays. These substances, essential for plant health, are also beneficial for humans, providing antioxidant qualities that can lower the risk of heart disease, cancer, and neurodegenerative diseases when consumed in foods like berries and apples. They have been used in herbal medicine for their anti-inflammatory and anti-cancer properties, making them a key focus in drug research. Flavonoids' dual significance in plant function and human health underscores them as a vital natural compound group [20]. The most significant flavanones are hesperidin, hesperetin, naringenin, naringin, and 2'-hydroxyflavone. Taxifolin is also an important flavanone. Flavanones, which are structurally similar to flavonols, have the ability to block the production of MMPs, which in turn inhibits the invasiveness of tissues and the danger of metastases.

2.2.4 Isoflavonoids

Isoflavonoids are a subclass of flavonoids that are only present in plants that are members of the Fabaceae family. These plants include soybeans, red clover, and chickpeas, among others. They perform the function of secondary metabolites and are very important in the process of defending the plant against bacteria that might cause disease. Isoflavonoids are distinguished from other flavonoids in terms of their structural composition by the presence of a phenol group linked to carbon 2 rather than carbon 1 [16,23]. Isoflavonoids may be found in both glycosylated and aglycosylated forms; the primary isoflavonoids are Daidzein, Genistein, Glycitein, and Biochanin A. These molecules are also able to manifest themselves in a variety of glycosylated forms, such as B-glycisudem, 6″-O-malonyl-glycoside, and 6″-O-acetyl-glycoside [24].

Isoflavonoids have been demonstrated to have therapeutic potential in humans, with considerable study demonstrating their use in the prevention of a variety of disorders conditions including osteoporosis, diabetes, the Kawasaki syndrome, Alzheimer's disease, and cardiovascular disease are examples. In addition, they have the ability to fight free radicals by donating hydrogen atoms from benzylic ring-attached groups and by activating antioxidant enzymes such as glutathione, catalase, and superoxide dismutase. This gives them their antioxidant capabilities. Nevertheless, their anticancer capabilities represent their most substantial therapeutic promise. Isoflavones, which have a similar molecular structure to oestrogens, can attach to oestrogen receptors, which allows them to compete with cancer-causing oestrogens and lower their levels. Because of this, isoflavones have been the subject of a significant amount of research to determine their potential function in the treatment of breast cancer and other forms of cancer [20,24].

2.2.5 Flavanols

Flavanols, or Flavan-3-ols, feature fully saturated 1, 2, and 3 carbons with a hydroxyl group on the chiral carbon 2. Essential members include catechin, epicatechin, and epigallocatechin compounds-mostly found in tea, apples, cocoa, and chocolate [25]. Scientific evidence shows that flavanols can block enzymes like α-amylase and α-glucosidase in humans, leading to lower blood sugar levels. They are also proven to reduce blood pressure, lower the risk of heart disease, and act as antioxidants. Furthermore, flavanols might help fight depression and obesity [16].

2.2.6 Chalcones

Chalcones are a distinct subgroup of flavonoids that may be differentiated from other flavonoids due to the chemical structure of chalcones. The carbons represented by the numerals 1, 2, and 3 do not, in contrast to those represented by same numbers in other flavonoids, made a third ring in between the two benzene rings. Furthermore, chalcones have a ketone group located on the carbon atom that is shown by the number 3 in the picture. These open-chain flavonoids are abundant in a wide variety of plants, such as vegetables, fruits, grains, roots, flowers, teas, and wines, particularly those belonging to the families Moraceae, Leguminosae, and Compositae [26]. In this particular class of flavonoids, licochalcone A, phloretin, xanthohumol, and isoliquiritigenin are the primary flavonoids that are employed for therapeutic reasons [27].

Chalcones play a vital part in plant defense systems in the natural world. They do this by neutralizing reactive oxygen species (ROS), which stops molecular damage and protects against assaults by pathogens. Chalcones, a group of chemical compounds, exhibit a range of health benefits, including antifungal, anti-inflammatory, and antibacterial properties, as well as the ability to inhibit cancer growth and protect brain neurons. Their potential for new pharmaceuticals is significant, primarily due to their role in reducing reactive oxygen species (ROS). These damaging molecules can wreak havoc on cells when uncontrolled, but chalcones help regulate oxidative balance, contributing to their wide-reaching medical efficacy. Research is ongoing to delve deeper into how chalcones work and to utilize their full therapeutic promise for human health [28].

2.2.7 Anthocyanidins

An unsaturated ring that forms a flavylium cation 29 between the two benzene rings is what sets anthocyanidins apart as a group that exhibits substantial hydro solubility. The pigments found in leaves, flowers, vegetables, and fruits are rich in flavonoids, which are responsible for the variety of hues that include purple, red and blue. In addition to being pigments, anthocyanidins have strong antioxidant qualities and control the physiological processes of plant tissues. Delphinidin, cyanidin, peonidin, malvidin and pelargonidin are the main anthocyanidins. It has been shown that anthocyanidins in humans have anticancer, anti-diabetic, anti-obesity, and neuroprotective properties. They also stop the proliferation of cancer cells [30].

2.3 Biological Availability

In spite of the fact that flavonoids as a whole are not poisonous and have a significant amount of therapeutic potential, the majority of flavonoid groups have a relatively poor bioavailability. This characteristic differs greatly across different compounds in almost every way. The bioavailability of isoflavones, flavanones, quercetin glucosides, and flavanols is greatest between all flavonoid subclasses; nevertheless, this is not enough for therapeutic applications [13]. Because of their low water solubility, most flavonoid groups, except for anthocyanidins, are difficult to absorb by oral administration, which in turn lowers their bioavailability and their therapeutic effect [31]. Anthocyanidins are the only flavonoid group that has a substantial water solubility. In addition, flavonoids have restricted intestinal permeability, quick breakdown in extremely acidic conditions, extensive metabolism, and poor stability, all of which contribute to the low bioavailability of these substances [9].

The limits in bioavailability are being addressed by investigating a variety of delivery system-based techniques, with a particular emphasis on either increasing stability or boosting intestinal absorption, as well as modifying the location of absorption [31–35]. In addition, the utilization of delivery methods may improve flavonoid solubility, decrease gastrointestinal degradation, augment bloodstream absorption, defend alongside kidneys clearance, and shield in opposition to liver secretion. As a direct result of this, exploring flavonoid-based delivery methods has gotten substantial significance in the scientific community [31-35].

2.4 Smart Delivery of Drug

In the fight against cancer, many flavonoid-based delivery systems are now under development. One of these systems is specifically geared towards treating cervical cancer.

These new delivery methods make it possible to utilize smaller quantities of flavonoids and make it easier to make use of ligands that effectively direct malignant cells. This reduces the amount of harm that is caused to healthy cells while simultaneously improving the efficacy of the treatment. When it comes to encapsulating these pharmaceuticals, there are a lot of different delivery methods that may be explored. This will rely on the material that is selected as well as the characteristics of the drug. Consequently, the delivery methods may come in a wide variety of forms, the basic types of which are below.

3. System for the Administration of Lipids

Liposomes, firm lipid-created nanoparticles, and combinations are the three basic groups that fall under the umbrella term "lipid-based delivery systems." There might be other subgroups included within any of these categories [36].

3.1 Liposomes

Liposomes are circular vesicles that are often made up of emulsifiers as well as a bioactive substance that has been dissolved in an organic solvent. They normally consist of at least one layer of lipids, which enables them to often encapsulate both hydrophilic and hydrophobic medicines [37,38]. They have a lipid bilayer. Phospholipids make up the bulk of a liposome's composition, but the inclusion of cholesterol or a hydrophilic polymer for instance polyethylene glycol (PEG) is not out of the question. They are referred to as stealth liposomes when mixed with this kind of polymer, and they have a prolonged circulation period and better efficiency as a result. Because of the employment of phospholipids and cholesterol in liposomes, structural and biological stability is ensured. This results in biocompatible transport systems that have a high encapsulation efficiency for all kinds of flavonoids, often surpassing 80% and, in many instances, reaching over 95%. In addition, the stability of liposomes lessens the possibility of aggregation, lessens the risk of toxicity in therapeutic applications, and improves the capacity to manage the release of medications that are encapsulated. Despite this, they continue to display some degree of physical and chemical instability, which may result in aggregation problems over time and drug degradation while the substance is being stored [39–41].

Liposomes are preferred because of their proportions and polydispersity index (PdI), which typically adjust among 100 & 200 nanometers and between 0.1 and 0.25, respectively. Because of these qualities, they are able to readily spread through the pores of plasma vessels and concentrate in tumors, which often have a larger number of holes in the blood capillaries that surround them [39,40].

Studies both in vitro and in vivo have shown that there are several advantages to using liposome applications. These advantages are mostly attributable to the great ability of liposomes to encapsulate flavonoids, which results in improved therapeutic effects and minimal toxicity. After 24 hours of incubation, investigations conducted on cervical malignant cells lines (HeLa) reveal that encapsulating flavonoids into liposomes decreases the concentration required to produce a 50% inhibition (IC50) in cellular viability. This decrease is from a concentration of 200 M for free quercetin to a concentration of around 100 M after the same amount of time. When utilizing liposomes composed of triglycerides, lecithin, PEG, and folic acid, the IC50 may be reached at concentrations of 14 M [40,42]. This is possible when the incubation duration is prolonged. Associated to the direction of free quercetin, investigations conducted in vivo

suggest that quercetin-loaded liposomes consisting of PEG, cholesterol, and soybean phosphatidyl-choline may diminish the growth of a tumor by about three times as much [40,42]. More liposomes that include soybean plant phosphatidylcholine & cholesterol have shown a decrease in tumor volume of around fifty percent [38]. In the context of different types of cancer, the use of liposomes has also been the subject of research, with in vitro studies demonstrating high encapsulation rates, minimal toxicity, and high cell inhibition percentages [43,44]. In the treatment of cancer, researchers have experimented with a wide variety of emulsifiers, such as lecithin and PEG derivatives. In other cases, chitosan coatings are investigated in an effort to improve bioavailability and in vivo stability. This opens the door to new opportunities for enhancing these systems' utilization in research on cervical cancer.

3.1.1 Nanoparticles Created from Lipids

Nanoparticles derived from lipids are another extensively researched delivery technology. These nanoparticles, known as solid lipid systems, exist as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) at room temperature. SLNs are fully solid with a perfect crystal structure, whereas NLCs exhibit an imperfect crystal structure, leading to systems with both solid and liquid regions. This results in a higher medication loading while reducing the amount of water present [39,43,43–46]. Compared to liposomes, SLNs do not need organic solvents; as a result, their cytotoxicity is decreased, and they can retain a high encapsulation capacity for both hydrophobic and hydrophilic medicines. As a consequence , SLNs provide great bioavailability, low-cost and simple manufacture on a wide scale, and the capacity to maintain regulated release [39]. Non-ionic surfactants including Polysorbate 80®, Poloxamer 188, and Tyloxapol are the primary components of both SLNs and NLCs. Phosphatidylcholine and lecithin are also present on occasion. The amphoteric character of these surfactants contributes to the increased system stability [47]. If of NLCs, liquid lipids such as oleic acid, olive oil, almond oil, and cetiol® are used in the production of the system's liquid component [39]. In spite of the many benefits they provide and their excellent tolerance in vitro and in vivo testing as a result of their natural composition, it is necessary to take into account the harmfulness of the surfactants and other excipients that are required for manufacturing. In addition, there is still the possibility that the particles may aggregate and recrystallize [36,48].

There has not been a comprehensive investigation of using SLNs and NLCs in cervical cancer-related in vitro and in vivo tests. However, trials in other forms of cancer have proved their promise, showing high encapsulation rates (more than 90%) and drug loadings that are larger than 10% and, in some instances, even greater than 20%. In vitro cell viability has been shown to drop significantly, while in vivo tests have shown dramatic reductions in tumor volume. Based on these results, the use of SLNs and NLCs in anticancer therapy aimed at cervical cancer may hold great promise and should be the subject of additional exploration [43,45,46,48–51].

3.2 Emulsions and Nanoemulsions

Emulsions and nanoemulsions are two more forms of delivery systems that may be found in addition to the two systems described above. These systems take advantage of the interaction between water and oils by adding an emulsifier, such as polyglyceryl-10 laurate or PEG 660-stearate, to generate structures that help in solubilizing flavonoids and enhancing their bioavailability [52,53]. In doing so, these systems form structures that can form structures that

help solubilize flavonoids. The application of emulsions and nanoemulsions results in high rates of flavonoid encapsulation, typically greater than 80%, with reduced aggregation and avoidance of gravitational separation [52]. This is despite the fact that neither type of emulsion is a thermodynamically stable system, and that both dissociate over time. Emulsions may be distinguished from nanoemulsions based on their size, with emulsions having sizes more than 200 nm and nanoemulsions having sizes lower than 200 nm. To generate systems with acceptable size ranges that can more readily reach and accumulate at the target site, various ratios of emulsifiers may be examined depending on the desired delivery site for the flavonoids [54]. These ratios can be evaluated to develop systems with appropriate size ranges.

At a concentration of 200 g/mL, nanoemulsions made of soybean phosphatidylcholine and cholesterol were evaluated in cervical cancer cells, and the results showed that the viability of the cells was only reduced by 10%. On the other hand, they showed a low level of toxicity, which calls for further research to be done in order to maximize their therapeutic potential [52]. In different forms of cancer, emulsions and nanoemulsions have shown comparable physical features in terms of size, encapsulation rate, and stability, but with a strong anticancer potential, as proven by a large drop in viable cells. Nanoemulsions have also shown that they can encapsulate a higher concentration of cancer-fighting agents. For instance, a substantial decrease was seen in melanoma cells at concentrations of medication encapsulated in lecithin, castor oil, and PEG 660-stearate emulsions that were higher than 50 M. At concentrations of 25 M medication encapsulated in a Labrasol®/Tween®, lecithin, and Miglyol® 812 emulsion, a decrease in viability of about 60% was observed in human colorectal cancer cells [55]. In order to improve flavonoid encapsulation, boost their anticancer effects, and raise the therapeutic index, several formulations that include novel emulsifiers and varied ratios might be investigated. The development of anticancer medicines based on these compounds may make great headway if approached in this manner.

3.3 Nanoparticles Derived from Polymers

The use of polymers has often accomplished encapsulation of flavonoids. Polymer-delivery methods were among the earliest vectors to be used and were also one of the most investigated. The described delivery systems use nanoparticles and polymer-coated, hydrophobic surfactant cores to transport flavonoids in the body. These structures boost flavonoid stability, preventing degradation during transport, and enhance their solubility, aiding absorption, especially as flavonoids tend to be water-repellent. By improving bioavailability, these systems ensure flavonoids are more effectively absorbed and utilized by the body, maximizing their therapeutic potential for health benefits. [55–57]. The development of this kind of system entails dissolving flavonoids in an organic molecule, which is commonly ethanol. The ethanol is then removed from the system by evaporation under vacuum, spray-drying, or freeze-drying in order to lower the system's cytotoxicity [37]. This process allows for the achievement of a high final concentration. These polymer-based nanoparticles may have very different properties depending on the polymer type, which can be classified as natural, synthetic, or inorganic-based polymers [36]. The properties of these nanoparticles can change quite a bit.

3.3.1 Polymers Obtained from Natural Sources

In the case of biopolymers, systems based on natural polymers, also known as biopolymers, generate extremely diverse systems depending on the materials utilized in their composition. These materials include proteins and polysaccharides [36,37]. The application of these polymers in in vitro and in vivo testing has been the subject of significant study [58–60]. The polymers guarantee good biocompatibility and biodegradability, in addition to minimal cytotoxicity. However, systems that are based only on proteins or polysaccharides are not very popular. The use of a mixture of one biopolymer with either a synthetic or an inorganic-based polymer is something that is explored in many different situations. The conjugation of a polysaccharide, such as chitosan, with a protein, another polysaccharide, or another kind of polymer is a relatively frequent practice. Chitosan is one example of this. This methodology results in systems that are more biocompatible, biodegradable, and stable than those achieved by other methods. Chitosan also has mucoadhesive characteristics, which contribute to the increased delivery of systems to mucosal target locations [58,59,61,62]. Because of this, conjugating a biopolymer with another kind of polymer is common, resulting in systems that have improved performance for both in vitro and in vivo experiments. In general, the size of these systems is less than 200 nm, they have a high level of stability, and they have a regulated drug release, all of which assist transport to the cells of interest [58,63–65]. Natural polymeric systems that are based on polysaccharides have been shown to be a key way of increasing the bioavailability of systems [66–68]. These systems are often employed in conjugation with other polymers or inclusion complexes.

On cervical cancer cell lines, the usage of proteins such BSA (bovine serum albumin), silk fibroin, keratin, and gliadin was evaluated for its potential to treat the disease. Only silk fibroin has been employed, with no other related compounds at all, and this is mostly because of the copolymeric structure of silk fibroin, which contains both hydrophobic and hydrophilic blocks. These blocks promote flavonoid encapsulation and increase the stability of flavonoids [64,69]. Nevertheless, in comparison to other systems, the size of this silk fibroin-based polymeric system was rather big, and its IC50 concentration was relatively high, coming in at 250 g/mL [59]. The use of polysaccharides in cervical cancer focused on chitosan conjugated with another polymer, such as quinoline or gliadin, as well as the straightforward use of fucoidan, a polysaccharide with chitosan-like properties, which exhibited a relatively low IC50 of 20 g/mL despite its considerably large size of 221 nm [64]. In addition to the size reduction that occurs as a consequence of the conjugation of different kinds of polymers, this conjugation also increases the encapsulation rate, which is normally somewhere around 80% and is more than the encapsulation rate of 21.81%.

3.3.2 Manufactured Polymers

PEG is the most common form of synthetic polymer used in the production of nanoparticles, which belong to another category of polymer-based nanoparticles. PEG is often employed with other methods to produce a higher encapsulation rate and improve flavonoid solubility [59,70]. PEG-based systems often have a high rate of encapsulation, typically more than 90%, despite the fact that they exhibit a low rate of degradation and a poor compatibility [57,70–72]. However, these negative effects may be considerably reduced by constructing systems that are

formed of a combination of polymers, making using these polymers feasible in in vitro and in vivo studies [57,70–72].

In vitro and *in vivo* investigations on anticancer medicines for the treatment of cervical cancer have previously been carried out. These studies used formed PEG systems coupled with poly lactide-co-glycolide, poly e-caprolactone conjugated with PEG 1000 succinate, and gelatine modified pluronic systems [70,73,74]. In addition, a variety of additional carriers, including other kinds of chemicals that were conjugated with PEG or its derivatives, were investigated and evaluated. The portion of the article that discusses this kind of chemical includes a discussion of several systems in which PEG is not the primary constituent. Due to the high blood circulation duration that these systems attain, cell viability studies reveal that it is feasible to produce lowered IC50 values close to 10 M utilizing systems that consist of just synthetic polymers, namely those constructed of PEG and poly lactide-co-glycolide. They also show a high capacity to be conjugated with certain ligands, such as folic acid, which enables the active targeting of systems toward cancer cells. This is because cancer cells have more folic acid receptors than healthy cells [75]. The usage of systems including poly e-caprolactone and PEG 1000 succinate exhibited a decrease in tumor weight that was four times larger than that which was achieved by administering the medication in its free form in in vivo tests [74].

3.3.3 Inorganic Polymers

There is a wider variety of uses for delivery systems built on inorganic polymer bases [76]. Hyperthermia, targeted medication administration, tissue regeneration, and magnetic resonance imaging are a few of these uses. The majority of these carriers are composed of nanoparticles of iron oxide, copper, and gold oxide, which when mixed together most often create delivery systems in the form of nanoparticles or nanotubes [76–80]. These systems exhibit limited stability and biocompatibility, an elevated aggregation capacity, and oxidation, although these drawbacks are greatly mitigated by their covering with polymers like PEG. By offering a location for the binding of ligands and flavonoids, this coverage makes these systems feasible [76].

The widths of inorganic polymeric carriers are usually less than 50 nm, with encapsulation rates ranging from 70 to 80% [76–80]. These vehicles stand out from other kinds of systems due to their very small size. Researchers have experimented with coatings of iron oxide magnetic nanoparticles with BSA, a-cyclodextrin, citric acid, poly citric acid, PEG, or 3-aminopropyl triethoxysilane to transfect HeLa cells [76,78,81]. Depending on the method used, cell viability tests varied greatly; an IC50 of 10 g/mL was reached for the process mediated by BSA- and iron oxide-based nanoparticles [69].

The use of polymeric carriers in the treatment of various malignancies has also been the subject of much investigation, with numerous different approaches attempted to encapsulate flavonoids and direct them to cancer cells. A variety of polymers are emphasized, including PEG and chitosan, both of which were discussed before [72,82]. It has been investigated whether incorporating chitosan into the formation of systems and its conjugation with the vast majority of polymers can improve encapsulated flavonoids' stability and solubility [83,84]. The most common conjugation of chitosan is tripolyphosphate, and functionalization with PEG or some other type of inclusion complex has also been investigated. Poly(lactic acid), poly(lactic-co-glycolic acid), and polycaprolactone have also been investigated, and these systems are

generally conjugated with PEG or one of its derivatives [85–88]. In addition to the previously listed compounds, poly (lactic acid), poly (lactic-co-glycolic acid), and polycaprolactone have also been investigated. In vitro experiments that were mediated by these systems revealed a reduction in cell viability comparable to that observed in in vitro studies on HeLa cells. This finding indicates that this kind of system has a high degree of application for a wide variety of cancer cells.

For the purpose of encapsulating flavonoids and directing them to cancer cells, especially cervical cancer cells, polymeric carriers derived from natural, synthetic, and inorganic polymers have shown promise. These systems have the potential to provide a number of benefits, including greater targeting of cancer cells, higher solubility, stability, and bioavailability of the flavonoids, and increased bioavailability. The precise kind of cancer and the qualities of the final delivery system that are required, such as its size, encapsulation rate, and biocompatibility, have a role in the decision about which polymer to use and which conjugation approach to implement.

3.3.4 Micelles

Micelles, which are made up of amphiphilic molecules, may be divided into two distinct categories, polymeric micelles and lipid micelles, based on the composition of these molecules [36,89,90]. Micelles, because of their hydrophobic core, are well suited for encapsulating medicinal compounds like flavonoids that have a low solubility but a high hydrophobicity. Increased bioavailability is the result of the hydrophilic outer component of micelles, which offers protection and stability [83].

Micelles offer several benefits, including their tiny size (typically below 100 nm), excellent thermodynamic stability, high drug loading capacity, enhanced cellular uptake, and ease of synthesis on a wide scale. Micelles also have a high drug loading capacity. To improve the formulation, however, determining the appropriate component ratio might need a lot of research [83].

In vitro experiments on cervical cancer cells using micelles composed of cholesterol and chondroitin sulfate showed a 20% reduction in cell survival at a dose of 200 g/mL. These micelles demonstrated a considerable drug loading percentage (30.6% and 23.4%, respectively), while having a comparatively low encapsulation percentage [91]. Micelle-based in vitro experiments on various cancer forms revealed much-improved outcomes, with IC50 values of 110 M and 21.24 M in breast cancer and lung cancer cells, respectively. These investigations also revealed more favorable physical features of the micelles, including diameters lower than 100 nm and encapsulation efficiencies higher than 80%. Micelles have been proven in vivo experiments to have the ability to diminish the growth of tumors by more than three times when compared to free flavonoids [89,90,92–95].

In conclusion, using micelles as a vehicle for flavonoid encapsulation and delivery in cervical cancer calls for more research and optimization. If the quality of these systems are improved, then their performance as targeted delivery vectors may be improved as well. This will have important consequences for the therapeutic potential of these systems in the fight against cervical cancer.

3.4 Complexes Involving Inclusion

One kind of delivery system known as an inclusion complex is one in which the host molecule has the ability to ensnare another molecule via the use of non-covalent forces. This feature is what gives inclusion complexes their name. Because flavonoids are able to form hydrophobic contacts with these complexes, flavonoids have the ability to get "trapped" inside of these structures [95]. The main advantage of inclusion complexes is their cone-shaped structure, which is open on both sides and has hydrophilic and hydrophobic surfaces on the outside and interior, respectively. Because of this, flavonoids have the potential to get "trapped" in the internal cavity, which significantly contributes to the enhancement of their soluble, stable, and bioavailable states [68]. Inclusion complexes do, however, have several drawbacks, the most notable of which is a restricted capacity for encapsulating bigger flavonoids, such as glycosylated molecules. In addition, they often have a size that is higher than 200 nm, which makes it difficult to employ them for regulated administration in in vitro and in vivo experiments [96–98]. Following this, its application is somewhat constrained as a result of its limited adaptability and the fact that there are other techniques of flavonoid encapsulation that are less expensive.

Cyclodextrins make up the bulk of this category of delivery methods; among them, cyclodextrins are by far the most frequent. They may be changed to bring about modifications in their chemical and physical properties, which results in the creation of systems that are more appropriate for the delivery site. Cyclodextrins have the ability to change their characteristics chemically, giving them the ability to have more or fewer positive or negative charges, as well as a larger or lesser degree of replacement. Although there are numerous varieties of -cyclodextrins, -cyclodextrin, carboxymethyl-cyclodextrin, sulfobutyl ether--cyclodextrin, and hydroxypropyl--cyclodextrin are the most often utilized in research. It is possible to conjugate cyclodextrins with polymers like chitosan to increase their stability, shrinkage, and bioavailability. Furthermore, since biotin's receptors are widely expressed in cancer cells, conjugation with biotin is quite common and may help efficiently target cancer cells. This explains part of the widespread occurrence of conjugation with biotin. Periodically, the ability of other delivery methods, such as -cyclodextrins, -lactoglobulins, and -cyclodextrins, to encapsulate flavonoids is also investigated [68,96–100]. In vitro experiments on HeLa cells using inclusion complexes consisting of -cyclodextrin with a chrysin concentration of 100 M show a reduction in viability to 11.5% during a 48-hour incubation period. Inclusion complexes were used in these experiments. The vitality of cells was significantly reduced when flavonoids were used in other cancer-related studies, as opposed to when they were used in their free form [68,96–100]. Thus, the use of inclusion complexes for flavonoid loading/encapsulation and delivery can be investigated, even though the previously mentioned drawbacks must be carefully considered, because they readily facilitate flavonoid solubilization in aqueous solutions, where most of them cannot be dissolved. This is true even if it's important to consider the drawbacks that have previously been discussed.

3.5 Different Kinds of Delivery Methods

It is possible that other kinds of delivery systems, like as dendrimers, may serve as alternatives for encapsulating flavonoids and delivering them specifically to cancer cells [101]. A class of polymeric polymers known as dendrimers have a highly branching architecture,

several functional groups, and an interior cavity that may encapsulate drugs like flavonoids. It is these poly (amidoamine) (PAMAM) dendrimers that have drawn the most interest from scientists. These dendrimers have been put to the test in a variety of in vitro cancer tests, where they have shown promising outcomes. For instance, they were able to lower the viability of HeLa cells to forty percent by employing a baicalin flavonoid concentration of twenty-five micrograms per milliliter [76,102,103].

However, there are restrictions placed on the use of dendrimers because of safety concerns over their toxicity. In order to lessen the severity of these effects and foster a more fruitful connection with certain ligands, several strategies, such as PEG conjugation, have been mulled over [76,103]. In the future, more research will be necessary to create new tactics that will assure an improvement in the stability and bioavailability of dendrimer-based systems. This will increase their efficacy in encapsulating flavonoids and delivering them to target cells, which may lead to improved results from cancer therapy.

Despite recent developments in treatment and research, cancer continues to be one of the major causes of mortality worldwide. Because there is currently no therapy that is shown to be successful against cervical cancer, it is imperative that new procedures be developed for the purpose of improving therapeutic results. Innovative cancer treatments are being developed with the intention of providing treatment options that are effective, less intrusive, and more cost-effective.

3.6 Future Perspectives

The potential benefits of flavonoids for cancer treatment have been studied extensively in vitro and in vivo. Despite their low bioavailability, limited solubility, and degradability in acidic conditions, flavonoids have demonstrated substantial promise in treating cervical cancer by decreasing cell viability and tumor growth. Researchers are developing delivery systems for flavonoids that will enhance their stability, solubility, bioavailability, and targeted administration to cancer cells. In this way, flavonoids will have a greater chance of treating cancer effectively. In order to achieve these goals, research is being conducted on encapsulation systems conjugated to other materials and functionalized with certain ligands, such as folic acid. Researchers have investigated many different delivery systems for cancer therapy, but the ones that show the greatest promise are those that use lipids based on NLCs and those that use polymers of various kinds. In contrast to NLCs, polymeric systems offer good biocompatibility, controlled release, and significant reductions in cell viability and tumor growth. However, there is still room for improvement in research on polymeric systems, specifically the investigation of additional chemicals for polymeric conjugation to improve flavonoid solubility and stability.

4. Conclusion

In conclusion, it is crucial to conduct continuous research into the development of novel therapeutic techniques that can be used to treat cancer in the future. There is a need for further investigation and development regarding flavonoid encapsulation as a means of providing high-performance flavonoid delivery systems for cancer treatment since flavonoids are essential components of cancer cells. By increasing knowledge of various materials, conjugations, and functionalization of flavonoids, researchers may be able to develop effective and economical strategies for enhancing the anticancer effects of flavonoids. Further, researchers may also be

able to reduce the toxic effects of flavonoids on the cells in the body if they can find a way to do so. As a result, better therapeutic results will be achieved in the future.

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نظم توصيل الأدوية الذكية المعتمدة على الفلافونويد في علاج السرطان: أمل جديد للطب الدقيق

ياسر أنور

قسم العلوم البيولوجية، كلية العلوم، جامعة الملك عبد العزيز، جدة، المملكة العربية السعودية

yanwarulhaq@kau.edu.sa

المستخلص. تُعتبر الفلافونويدات مركبات بوليفينولية تمتلك خصائص قوية مضادة للسرطان. ورغم ذلك، فإنها غير مناسبة لعلاج السرطان بسبب انخفاض ذوبانها، وعدم استقرارها، وتوافرها البيولوجي المحدود. لتعزيز متانتها وتوافرها البيولوجي، تم اقتراح استخدام طرق توصيل تشمل الفلافونويدات كحل واعد. ستركز مراجعتنا على نظم توصيل الفلافونويد الواعدة للأدوية المضادة للسرطان، خاصةً في علاج سرطان عنق الرحم. بالإضافة إلى الإمكانيات العلاجية الهائلة للفلافونويدات، تُعتبر طرق التوصيل أمرًا حاسمًا لتحقيق نتائج إيجابية في علاج السرطان. ومع أن الفلافونويدات تتمتع بخصائص مضادة للسرطان، فإنها أيضًا مركبات بوليفينولية تحدث بشكل طبيعي. ومع ذلك، فإن هذه المركبات غير مناسبة لعلاج السرطان بسبب عدم ذوبانها، واستقرارها، وتوافرها البيولوجي. من خلال إضافة الفلافونويدات إلى نظم التوصيل، يمكن تعزيز خصائص هذه المركبات، مما يؤدي إلى زيادة توافرها البيولوجي ومتانتها. تُبرز البيانات المستخلصة الإمكانيات العلاجية الكبيرة للفلافونويدات وأهمية بناء آليات توصيل فعالة لمرضى السرطان لتحقيق نتائج جيدة. في الختام، قد توفر الفلافونويدات علاجًا أكثر كفاءة وتفصيلًا للسرطان عند دمجها في نظم التوصيل. يمكن أن تساهم طرق علاج سرطان عنق الرحم المعتمدة على الفلافونويد بشكل كبير في تحسين جودة حياة الملايين من النساء. من خلال احتواء الفلافونويدات في نظم التوصيل، يمكن تقليل الآثار السلبية للعلاج الكيميائي، مما قد يحسن من نتائج المرضى.

الكلمات المفتاحية: الفلافونويدات، مضادات السرطان، الجسيمات النانوية، توصيل الأدوية.