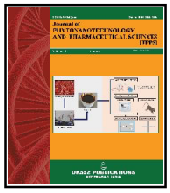
Journal of Phytonanotechnology and Pharmaceutical Sciences 4(4): 21-31, 2024

Online ISSN:2583-0376

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.54085/jpps.2024.4.4.4

Journal of Phytonanotechnology and Pharmaceutical Sciences



Review Article : Open Access

Critical review on harnessing phytochemicals for G-quadruplex stabilization: Implication for cancer therapy

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Article Info

Article history

Received 25 October 2024

Revised 1 December 2024

Accepted 2 December 2024

Published Online 30 December 2024

Keywords

G-Quadruplexes

Phytochemicals

Cancer therapy

Gene regulation

Telomere maintenance

Apoptosis

Flavonoids

Polyphenols

Abstract

Guanine-rich regions in both DNA and RNA combine to generate the distinctive nucleic acid structures known as G-quadruplexes (G4s). These structures are essential for controlling important biological functions such DNA replication, telomere maintenance, and gene expression. G4 formation dysregulation is associated with several types of diseases, including cancer. As a result, G4 targeting has become a viable therapeutic approach for the treatment of cancer. The potential of phytochemicals, which are naturally occurring substances present in plants, to stabilize G4 structures, has drawn a lot of interest. These chemicals have been demonstrated to bind and stabilize G4s, affecting gene expression and tumor cell proliferation. They also display a range of bioactivities, such as antioxidant, anti-inflammatory, and anticancer qualities. By specifically altering the stability of these structures in cancer cells, phytochemicals' potential to interact with G4s introduces novel therapeutic opportunities. It has been demonstrated that phytochemicals such polyphenols, flavonoids, and alkaloids may stabilize G4s and stop the action of G4-binding proteins, which are essential for the development and survival of cancer cells. These substances can promote death in cancer cells by interfering with vital processes including transcription, replication, and telomere extension by increasing G4 stability. This review explores the molecular mechanisms through which phytochemicals stabilize G-quadruplexes and their potential as therapeutic agents in cancer treatment. The implications of targeting G4 structures in cancer therapy, along with the challenges and future directions of using phytochemicals in clinical settings, are also discussed.

1. Introduction

G- quadruplexes (G4s) are unique nucleic acid secondary structures formed by guanine-rich sequences in DNA and RNA. These structures consist of stacked planar arrangements of four guanine bases held together by purine hydrogen bonding, forming what's known as G-quartets. Multiple G-quartets stack upon each other to form the complete G-quadruplex structure, which is typically stabilized by monovalent cations, particularly potassium (Sen and Gilbert, 1988). The presence of G4s in areas that control genome activity has suggested their involvement in various biological processes.

The discovery that G4-rich telomeric repeats create G4 structures indicated a potential mechanistic connection to telomerase-driven telomere elongation, leading to an investigation of G4 stabilizing compounds that could impede the proliferation of cancer cells by disrupting telomere upkeep. For example, the mouse regulator of telomere elongation helicase 1 (RTEL1) has been demonstrated to preserve telomere integrity by unwinding telomeric G4 structures. Telomeric G4s were initially proposed to hinder telomerase activity, but they could also play a crucial role in the recruitment of telomerase (Balasubramanian *et al*., 2020).

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The biological significance of G-quadruplexes has garnered substantial attention in recent years due to their presence in critical regions of the genome, including telomeres, promoter regions of oncogenes, and regulatory regions of various genes. These structures have been implicated in various cellular processes, including transcription regulation, DNA replication, and genomic stability. Research has shown that G-quadruplexes are particularly abundant in cancer-related genes, making them potential therapeutic targets (Balasubramanian *et al*., 2011).

Nutraceuticals, which are compounds found in food that provide medical or health benefits, have shown promising interactions with G-quadruplexes. Several plant-derived compounds have been identified as G-quadruplex-binding ligands. For example, certain flavonoids and polyphenols found in fruits and vegetables have demonstrated the ability to stabilize G-quadruplex structures. This interaction has potential implications for cancer prevention and treatment, as stabilizing G-quadruplexes in oncogene promoters can help regulate gene expression (Pagano *et al*., 2015). The structural interaction between nutraceuticals and G-quadruplexes typically involves π-π stacking interactions with the G-quartet planes and electrostatic interactions with the grooves of the G-quadruplex structure. These interactions can be further enhanced by the presence of specific functional groups in the nutraceutical compounds. For instance, EGCG (epigallocatechin gallate), a major component of green tea, has been shown to bind and stabilize certain G-quadruplex structures effectively (Wang *et al*., 2014).

G-quadruplex (G4) formation begins with the fundamental building block known as the G-quartet, which consists of four guanine bases

arranged in a planar configuration. These guanines are connected through Hogsten hydrogen bonding, forming a square arrangement. Each guanine both donates and accepts two hydrogen bonds, creating a highly stable structure. The stability is further enhanced by monovalent cations, particularly K^+ and Na^+, which coordinate with the O_6 atoms of the guanines and site either within the quartet planes or between them (Davis *et al*., 2004). The topology of G-quadruplexes is remarkably diverse and can be classified based on several key characteristics. The first distinction is the number of strands involved in the structure: G4s can be unimolecular (formed from a single strand), bimolecular (two strands), or tetramolecular (four strands). The orientation of the strands provides another crucial topological feature, leading to parallel, antiparallel, or hybrid conformations. This strand directionality is determined by the glycosidic bond angles of the guanines, which can adopt either syn or anti-conformations (Burge *et al*., 2006).

2. G-quadruplexes and cancer

G-quadruplexes (G4s) are crucial structural elements in cancer biology, playing a role in cancer development, progression, and potential therapeutic interventions. Their distribution is enriched in oncogene promoters compared to tumor suppressor genes, suggesting an evolutionary selection for these structures in cancer-related genes, leading to intense research into their therapeutic targets (Balasubramanian *et al.*, 2011). G4 involvement in cancer is well-studied, with the c-MYC oncogene being a prime example. The nuclease hypersensitive element III1 (NHE III1) in the c-MYC promoter can form a transcriptional repressor, which can be stabilized by small molecules to decrease c-MYC expression. Similar regulatory G4 structures have been found in other cancer-related genes, highlighting their role in cancer biology (Yang *et al.*, 2006).

Telomeric G4s are crucial for cancer cell immortality, as they maintain telomere length through telomerase activation. Stabilizing G4 structures in telomeres has shown promise as anticancer agents, leading to the development of various G4-stabilizing ligands as potential telomerase inhibitors for cancer therapy (Neidle and Parkinson, 2012). G4s and DNA damage repair mechanisms are crucial in cancer, as cancer cells often exhibit genomic instability, and G4 structures can disrupt DNA replication and repair processes. Mutated helicases like BLM and WRN are associated with cancer predisposition syndromes, highlighting the importance of proper G4 regulation in maintaining genome stability and preventing cancer development (Brosh *et al.*, 2010).

2.1 Phytochemicals

Phytochemicals are bioactive compounds found in plants that offer health advantages to humans, serving as a significant source of new bioactive molecules. These substances contribute to the distinctive color, flavor, and aroma of the plants. Phytochemicals are crucial for a plant's survival and defend against different diseases and pests (Fais *et al.*, 2024).

Bioactive substances, such as vitamins and phytochemicals, are naturally occurring or manufactured compounds with various health benefits, including antiageing, heart disease prevention, and protection against chronic conditions like type 2 diabetes and cancer. Food bioactive, found in plant and animal sources like milk and dairy products, play a crucial role in immune responses. A well-rounded diet rich in macro and micronutrients, vitamins, minerals, and probiotics is essential for enhancing healthy immunity and preventing diseases caused by harmful pathogens and toxic substances. Clinical studies have shown positive effects of vitamins D and E, zinc, selenium, polyunsaturated fatty acids (PUFAs), flavonoids, bio-peptides, and probiotics in influencing the immune system. Creating tailored meal plans that incorporate these nutrients can lead to improved community health (Xavier *et al*., 2024).

2.2 Diversity of phytochemicals

Phytochemical diversity refers to the wide variety of bioactive compounds produced by plants, many of which have been studied for their potential interactions with G-quadruplexes (G4s). G-quadruplexes are unique secondary DNA or RNA structures formed by guanine-rich sequences. These structures are stabilized through purine hydrogen bonding and are implicated in key biological processes, such as gene regulation, telomere maintenance, and replication. Several classes of phytochemicals exhibit the ability to stabilize G-quadruplex structures, enhancing their potential as therapeutic agents for cancer, neurodegenerative diseases, and other conditions where G4s play a critical role. Phytochemicals from plants and their derivatives have shown potential in improving cancer treatment effectiveness due to their biological activities and ability to reduce side effects (Dexter *et al*., 2024).

2.3 Anticancer properties of phytochemicals

Research evidence shows that phytochemicals possess considerable antitumor properties. About 50% of cancer medications authorized between 1940 and 2014 are derived from natural sources or are directly based on them. This review outlines several notable anticancer phytochemicals in this context. These phytochemicals have undergone testing for anticancer effectiveness at both *in vitro* and *in vivo* stages. They have complementary and intersecting mechanisms to hinder the carcinogenic process by neutralizing free radicals, inhibiting the survival and growth of malignant cells, and reducing tumor invasiveness and angiogenesis (Choudhari *et al*., 2020).

2.4 Rationale for targeting G-quadruplexes with phytochemicals

G-quadruplexes (G4s) are DNA and RNA formations influenced by sequences rich in guanine, which are crucial for cellular functions like gene regulation, telomere upkeep, and DNA replication. Their unique structural characteristics make them attractive targets for therapeutic strategies, particularly in cancer therapy. Light-activated photochemical can regulate G4 structures by attaching to them, causing DNA damage or hindering helicases that uncoil these formations, obstructing cellular processes like replication and transcription. This focused interaction reduces harm to healthy tissues. G4 ligands have been used as photosensitizers in cancer photodynamic therapy (PDT), triggering oxidative DNA damage and genomic instability in cancer cells. Photochemical aimed at G4 can also be formulated to engage with specific G4 formations linked to oncogenes, like KRAS, regulating oncogene expression, resulting in reduced tumor growth and enhanced survival rates in preclinical models. Thus, directing photochemical at G-quadruplexes offers a promising approach for cancer treatment, utilizing the unique structural characteristics of G4s for targeted and regulated therapeutic outcomes (Asamitsu *et al*., 2019).

G-quadruplex (G4) oligonucleotides represent more complex DNA and RNA secondary structures of great importance owing to their

involvement in various biological processes and disease conditions across different organisms. Strategies focused on adjusting human G4 structures and their associated functions are primary methods in current research seeking to discover new potential anticancer therapies or G4-based aptamers for diverse biomedical and biotechnological uses. Plants provide a wealth of phytochemicals that, in numerous instances, effectively bind and enhance the thermal stability of G4s, while also harbouring largely unexamined G4 motifs in their genome that may inspire innovative biotechnological approaches. In this document, we outline several G4 structures identified in plants, consolidating the current understanding of their functions and biological significance. Additionally, we examine several of the most promising G4 ligands derived from plant sources and discuss the established connections between these phytochemicals and G4-related biological activities, highlighting their potential as leads in the pharmaceutical industry (Falanga *et al.,* 2022).

Table 1: Phytochemicals and their roles in G-quadruplex stabilization and biological activities

Class	Examples	Properties	Reference
Polyphenols	Quercetin, resveratrol	Antioxidant, G4 stabilization	Yang *et al*., 2018
Alkaloids	Berberine, sanguinarine	Strong G4 stabilization	Wang *et al*., 2018
Terpenoids	Curcumin, saxol	Anticancer, promoter G4 stabilization	Chiara *et al*., 2021
Carotenoids	Beta-carotene, lycopene	Reduces oxidative stress	Kim *et al*., 2018
Glycosides	Ginsenosides, flavonoid glycosides	Anticancer, potential G4 interactions	Fehinti *et al*., 2021
Flavonoids	Kaempferol, luteolin	Anti-inflammatory, G4 targeting	Das *et al*., 2021
Phenolic acids	Caffeic acid, ferulic acid	Antioxidant, supports G4 stability	Carmen *et al*., 2022
Coumarins	Scopoletin, umbelliferone	DNA-binding, G4-interaction potential	Liu *et al*., 2021
Steroids	Diosgenin, withaferin A	Anticancer, telomeric G4 stabilization	Brassart *et al*., 2007

Table 2: The following table summarizes examples of anticancer phytochemicals

Phytochemical	Plant Source	Anticancer activity	Reference
Curcumin	*Curcuma longa*	Induces apoptosis, inhibits angiogenesis	Wilken *et al*., 2011
Resveratrol	*Vitis vinifera*	Antioxidant, inhibits cell proliferation	Ren *et al.*, 2021
Epigallocatechin gallate (EGCG)	*Camellia sinensis*	Induces apoptosis, prevents metastasis	Zhecheng *et al*., 2020
Lycopene	*Solanum lycopersicon*	Reduces oxidative stress, inhibits proliferation	Kapala *et al.*, 2022
Genistein	*Glycine max* (Soybeans)	Modulates epigenetics, induces apoptosis	Ahmad Jan *et al.*, 2022
Quercetin	*Allium cepa*	Promotes cell cycle arrest, induces apoptosis	Rauf *et al*., 2018
Podophyllotoxin	*Podophyllum peltatum*	Inhibits tubulin polymerization, DNA damage	Motyka *et al.*, 2023
Vinca alkaloids	*Catharanthus roseus*	Apoptosis by interfering with microtubules	Shawkat *et al.*, 2023
Apigenin	*Petroselinum crispum*	Inhibits proliferation, induces apoptosis	Rowles *et al.*, 2020
carotenoid	*Dacus carrota*	Antioxidant capacity	Rowles *et al*., 2020
Emodin	*Aloe vera*	Inhibiting proliferation induce apoptosis	Akkol *et al.*, 2021
Paclitaxel	*Taxus brevifolia*	Blocking cell cycle progression	Barbuti *et al.*, 2015
Gingerol	*Zingiber officinale*	Induce apoptosis	Nafees *et al.*, 2021
Allicin	*Allium sativum*	Induce cell apoptosis	Catanzaro *et al.*, 2022
Anthocyanins	*Vaccinium sect. cyanococcus*	Reduced cell proliferation	Lin *et al.*, 2016
Camptothecin	*Camptotheca acuminate decne*	Inhibiting DNA topoisomerase 1	Ghanbari *et al.*, 2021
Isoflavones	*Medicago sativa*	Stimulate apoptosis	Liang *et al.*, 2024

3. Phytochemicals

3.1 Flavonoids

Flavonoids, a significant category of phenolic compounds, demonstrated strong antioxidant properties. These substances have been linked to lowering the risk of major chronic illnesses and are predominantly found in fruits, vegetables, and various plant-based foods. Over 4000 varied flavonoids have been identified. They commonly possess a general framework that includes two aromatic rings (rings A and B) linked by three carbons, often in an oxygenated heterocyclic ring or C ring. Flavanols, flavones, flavanols (catechins), anthocyanidins, and isoflavonoids are distinct types of flavonoids due to the differences in the overall structure of the heterocyclic C ring (Mollakhalili *et al.,* 2017).

3.1.1 Quercetin

Quercetin and several of its glycoside derivatives have been extracted from numerous plants, including *Allium cepa*, *Aloe barbadensis*, *Brassica oleracea*, *Euphorbia helioscopia*, *Solanum*, *Malus pumila*, *Vitis vinifera*, and *Aronia mitschurinii* (Mateus, *et al.*, 2018). Quercetin interacts with G4 structures *via* π-π stacking interactions and hydrogen bonds, especially stabilizing G4s in telomeric areas and promoters of oncogenes such as c-MYC, π-π stacking quercetin features a flat aromatic structure that allows it to engage with the flat G-tetrads of the G-quadruplex *via* ð-ð stacking. These interactions are crucial for maintaining the structure's stability, quercetin accumulates on the terminal G-tetrads of the quadruplex. The ð-ð stacking enhances the structural stability of the G-quadruplex by reducing the system's entropy.

Hydrogen interactions, hydroxyl groups on the aromatic rings of quercetin might create hydrogen bonds with the phosphate backbone or bases in the quadruplex. Increase the attraction of quercetin toward the G-quadruplex., and aid in the precision of attachment to specific G-quadruplex structures. Electrostatic forces quercetin's negative charge at physiological pH (resulting from the deprotonation of its hydroxyl groups) is capable of electrostatic interaction with the positively charged cations (such as Kz) found within the G-quadruplex (Tawani *et al*., 2017).

Quercetin stabilizes G-quadruplexes in telomeres, hindering telomerase from lengthening telomeres in cancerous cells. This results in replicative senescence and cell death. Oncogene Inhibition in quercetin stabilizes G-quadruplex structures in oncogene promoters (such as c-MYC), decreasing transcriptional activity and suppressing tumor development. Induction of DNA Damage is Stabilized G-quadruplexes may obstruct DNA replication and repair mechanisms, leading to apoptosis in cancerous cells (Tang *et al*., 2020).

3.1.2 Apigenin

Apigenin is a dietary flavonoid present in various plants, including, *Petroselinum crispum* (parsley), *Apium graveolens* (celery), *Apium graveolens var. rapacious* (celeriac), basil, chamomile tea, and fruits and vegetables like kumquats (Oliver *et al*., 2018). Apigenin engages with G4 structures *via* π-π stacking and hydrogen bonds, demonstrating a preference for G4 DNA rather than duplex DNA. Linking through π-π stacking G-quadruplexes are maintained by guanine tetrads (G-tetrads), flat configurations created through purine hydrogen bonding among guanine bases. Apigenin, a flavonoid featuring a flat aromatic structure, engages with G-tetrads through π-π stacking interactions. This engagement enhances the stability of the G4 configuration. Hydrogen bonds and electrostatic Forces in Apigenin contains hydroxyl groups that can create hydrogen bonds with the phosphate backbone or bases of G4 DNA. Electrostatic interactions between the negatively charged phosphate backbone and the polar groups of apigenin further strengthen binding. Thermodynamic stabilization of apigenin to the G-quadruplex elevates its melting temperature (Tm), indicating enhanced thermodynamic stability. This stabilization may prevent the unfolding of G4 structures during biological activities such as transcription or replication. Selectivity toward G4 structures Apigenin displays a greater attraction to G-quadruplex structures than to duplex DNA. This selectivity is essential for its potential as a therapeutic agent aimed at oncogene promoters like c-MYC or hTERT (Nimal *et al*., 2024).

Biological effects of apigenin are regulation of transcription numerous oncogenes (such as c-MYC, KRAS, and hTERT) contain G-rich sequences in their promoter areas capable of forming G-quadruplexes. The stability of these structures through apigenin can obstruct the transcription of these genes, resulting in diminished expression of oncogenic proteins. Inhibition of telomerase apigenin can stabilize the G-quadruplex in telomeric regions, potentially blocking telomerase activity. This is especially important in cancer cells, where telomerase activity increases to preserve telomere length and encourage unregulated division. Antiproliferative action by stabilizing G-quadruplexes, apigenin could trigger DNA damage responses or impede replication fork movement in cancer cells, resulting in cell cycle arrest or apoptosis (Choudhari *et al*., 2020).

3.1.3 Genistein

It can be found in plants such as *Lupinus* (lupine), *Vicia faba* (fava beans), soybeans, coffee, *Pueraria* (kudzu), *Psoralea*, *and Flemingia vestita* (Singh *et al*., 2022). Inhibition of telomerase genistein has demonstrated the ability to decrease telomerase activity, possibly *via* indirect pathways or by directly interacting with G-quadruplex formations. Engagement with G-Quadruplex DNA although direct experimental proof is scarce regarding genistein's binding to G-quadruplex structures, computational analyses, and related compounds indicate that its planar configuration enables interaction with quadruplexes, promoting stacking with guanine tetrads. Gene expression regulation genistein may inhibit the transcription of essential genes related to proliferation and angiogenesis by stabilizing G-quadruplexes in the promoters of oncogenes. Induction of DNA damage are stabilized G-quadruplexes can disrupt replication and transcription processes, resulting in DNA damage and apoptosis in cancerous cells (AikKi *et al*., 2012).

Genistein reduces VEGF expression by stabilizing G4s in the VEGF promoter, thereby hindering angiogenesis in tumors and demonstrating antiproliferative properties Genistein induces cell cycle arrest and apoptosis through multiple pathways, including G-quadruplex stabilization and tyrosine kinase inhibition (Zhang *et al*., 2013).

3.2 Terpenoids

Terpenoids, a group of secondary metabolites from plants, have been studied for their potential anticancer and medicinal properties. Some terpenoids inhibit tumor development by promoting cell cycle

arrest, hindering cell differentiation, and stimulating apoptosis. In advanced stages, they suppress angiogenesis and metastasis by affecting intracellular signalling pathways (Kamran *et al*., 2022).

3.2.1 Curcumin

Curcumin, a yellow polyphenolic compound derived from the rhizome of *Curcuma longa* (turmeric), contains a turmeric oil that is made up of terpenoids (Paucar *et al*., 2022). Curcumin demonstrates a high binding affinity for G-quadruplex structures, mainly interacting *via* π-π stacking with the terminal G-tetrads. This interaction strengthens the stability of the G-quadruplex, reducing its likelihood of unwinding. Research shows that curcumin has a higher binding affinity for G-quadruplex DNA compared to double-stranded DNA, implying a level of selectivity that benefits therapeutic targeting. Telomeric areas that safeguard chromosome ends may create G-quadruplex formations. The stabilization of these structures by curcumin has been demonstrated to inhibit telomerase activity, an enzyme that lengthens telomeres in cancer cells, thus restricting the replicative capacity of these cells. The promoter area of the c-MYC oncogene has a sequence capable of forming a G-quadruplex, which functions as a transcriptional repressor. Curcumin's attachment to this G-quadruplex increases its stability, resulting in the repression of c-MYC transcription. This reduction can induce apoptosis in cancer cells, as seen in research using triple-negative breast cancer cell lines. Biophysical investigations, such as circular dichroism and thermal melting tests, have shown that curcumin enhances the thermal stability of G-quadruplex formations. This stabilization is thermodynamically advantageous, as negative Gibbs free energy (ÄG) values suggest spontaneous binding (Jha *et al.,* 2016).

Curcumin attaches to telomeric G-quadruplexes, preventing telomerase from extending telomeres, potentially leading to telomere shortening and senescence or apoptosis of cancer cells. Curcumin hinders transcription by stabilizing G-quadruplexes in oncogene promoters (such as c-MYC), leading to decreased proliferation of cancer cells. The interference with cancer cell survival strategies *via* telomerase inhibition and oncogene downregulation initiates programmed cell death (Roy *et al*., 2021)

3.2.2 Ginsenosides

Ginsenosides are a class of triterpenoids, categorized as a type of saponin, sourced from ginseng species like *Panax ginseng*, *Panax quinquefolium*, and *Panax notoginseng* (Yao and Guan, 2022). The method through which ginsenosides, especially ginsenoside compound K(CK), stabilize G-quadruplex (G4) formations is as described.

CK associates G4 DNA through electrostatic interactions and hydrogen bonds, facilitating G4 formation and increasing stability. CK raises the melting temperature (Tm) of G4 structures, signifying enhanced stability and mainly stabilizes G4 structures instead of duplex DNA because it is structurally compatible with the G4 shape. G4 structures in gene promoter areas, hindering RNA polymerase function and lowering transcription, especially oncogenes such as MYC and KRAS, CK reduces their expression, enhancing its therapeutic efficacy (Zhang *et al*., 2021).

The biological effects of ginsenosides inhibit telomerase function and reduce oncogene expression, aiding in their cancer-fighting abilities. Malignant tumor cells possess an unchecked capacity for growth and a high ability to invade, enabling them to spread by penetrating nearby tissues and infiltrating healthy cells. Invasion and metastasis are key elements influencing the survival of cancer patients. In recent years, numerous studies have demonstrated that ginsenosides can hinder various tumor cell types through different mechanisms, including proliferation, invasion, and migration (Yang *et al*., 2024).

3.3 Alkaloids

Alkaloids represent a class of organic compounds featuring ring structures that contain nitrogen and exhibit a broad spectrum of anticancer properties. These compounds contribute to cancer inhibition by blocking the activity of the enzyme topoisomerase, which plays a role in DNA replication, triggering apoptosis and activating the expression of the p53 gene. Nonetheless, alkaloids have existed long before humans, a number of them share structural similarities with neurotransmitters found in the human central nervous system. Given the therapeutic significance of alkaloids and studies detailing their function in combating uncontrolled cell growth, they could serve as a potent chemo-preventive agent in the age of contemporary drug development (Ouyang *et al.,* 2014).

3.3.1 Berberine

Berberine is a natural agent for lowering cholesterol and an alkaloid found in various plants like *Berberis aristata*, *Berberis vulgaris*, and *Coptis chinensis* (Momtazi *et al.,* 2017). The capacity of berberine to bind with c-MYC G-quadruplex differed from its capacity to bind with HIF1α G-quadruplex. Both binding types included π-π stacking. The stoichiometric ratios for berberine with c-MYC G-quadruplex were 1:1, 1:3, and 3:1, while for berberine with HIF1α G-quadruplex, it was only 1:1. Temperature significantly influenced the binding of berberine to c-MYC G-quadruplex. Berberine may enhance the thermal stability of c-MYC and HIF1α G-quadruplexes. Berberine suppressed the gene transcription and protein levels of c-MYC and HIF1α in colon cancer HCT116 cells. In vivo, berberine slowed tumor growth and reduced the protein levels of c-MYC and HIF1α. Twelve differential metabolites, including reduced adenosine triphosphate, were identified, suggesting that berberine may influence the metabolic pathways of the tricarboxylic acid (TCA) cycle and glycolysis/ gluconeogenesis, among others (Wen *et al*., 2022). Berberine selectively attaches to G4 DNA within oncogene promoters such as c-KIT and VEGF. Its flat configuration promotes π-π stacking with G-tetrads, and its cationic characteristic engages with the negatively charged phosphate backbone.

Berberine attaches to G-quadruplexes mainly by inserting itself between the G-quartets in the structure of G-quadruplexes. This indicates that berberine places its flat structure between the stacked guanine bases of the G-quadruplex, mainly engaging with the stacking area of the G-quartets. The planar aromatic rings of berberine snugly fit between the aligned G-quartets, establishing π-π stacking interactions with the aromatic rings of the guanine bases. These interactions reinforce the overall configuration of the G-quadruplex. The π-π stacking interactions among the aromatic rings of berberine and the guanine bases aid in the entropic stabilization of the G-quadruplex, enhancing its resistance to unwinding by DNA helicases and other destabilizing influences.

Besides π-π stacking, electrostatic interactions contribute to the binding process as well. Berberine has multiple nitrogen atoms in its

structure that can create hydrogen bonds with the oxygen and nitrogen atoms found in the guanine bases of the G-quadruplex. These electrostatic forces aid in enhancing the binding stability and add to berberine's overall affinity for G-quadruplexes. The nitrogen atoms in berberine that carry a positive charge might engage with the phosphate backbone of DNA, enhancing the binding affinity *via* electrostatic attraction. This improves the overall stability of the G-quadruplex structure (Li *et al*., 2023). Berberine reinforces G-quadruplexes in telomeric zones, hindering telomerase activity and resulting in telomere reduction, thereby aiding in the demise of cancer cells (Almatroodi *et al.,* 2022).

3.3.2 Camptothecin

Camptothecin, initially documented in 1966, is an indole alkaloid derived from monoterpenes. It is produced for commercial purposes from plants, primarily *Camptotheca acuminata* and *Nothapodytes nimmoniana* (Mohinudeen *et al*., 2021). Camptothecin has been demonstrated to attach to G-quadruplex formations, especially in DNA areas abundant in guanine bases. This binding may stabilize the G4 structure by inhibiting its unfolding, which typically happens during DNA replication or transcription. The main function of camptothecin is to block Top1, which plays a role in alleviating DNA supercoiling during transcription and replication. Top1 usually engages with DNA in areas that could create G4 structures. By stabilizing G4 structures, camptothecin might hinder Top1 from executing its function properly, resulting in DNA damage, replication stress, and cell death. In the telomeric areas of chromosomes characterized by plentiful G-rich sequences, camptothecin could promote the development of G-quadruplexes. Stabilizing telomeric G4 may hinder the function of telomerase (the enzyme responsible for preserving telomere length) or interfere with the usual telomere elongation process, crucial for the proliferation of cancer cells. Camptothecin's capability to stabilize G-quadruplexes may allow it to act synergistically with other drugs or compounds that target G4 structures, possibly resulting in improved antitumor effects. Camptothecin stabilizes G4s at telomeres and promoters using stacking and groove interaction (Miglietta *et al*., 2021).

4. Therapeutic implications of phytochemical-mediated G-quadruplex stabilization

4.1 Anticancer activity

Numerous phytochemicals have shown great promise in stabilizing G-quadruplex (G4) structures and exhibiting anticancer properties, making them promising therapeutic targets in the treatment of cancer.

4.1.1. *In vitro* studies

Numerous compounds derived from plants have been found to have exceptional G4-stabilizing qualities in recent studies. The isoquinoline alkaloid berberine has a dissociation constant (Kd) in the micromolar range and has been shown to selectively bind to G4 structures in telomeric DNA (Xiong *et al.,*2015*)*. Berberine treatment led to significant growth inhibition (IC_{50} = 2.5 μM) in a number of cancer cell lines, such as HeLa (cervical cancer) and MCF-7 (breast cancer) cells. In terms of G4 stabilization, EGCG (epigallocatechin gallate), the main catechin in green tea, has demonstrated encouraging outcomes *(*Majumder *et al*.,2024*)*. EGCG has been shown to bind to G4 structures with high affinity (Kd = 0.7 μM) and inhibit telomerase in a variety of cancer cell lines from 2024. While having little effect on healthy cells, the substance demonstrated selective cytotoxicity against cancerous cells.

Derivatives of curcumin have demonstrated considerable promise in G4 stabilization as well. (Pandya *et al*., 2020) found that against drug-resistant cancer cell lines, modified curcumin analogs exhibited strong antiproliferative effects and improved G4 binding characteristics (Kd = 0.3-1.2 μM).

Flavonoids and G4 stabilization, groundbreaking research has demonstrated that quercetin exhibits remarkable G4-stabilizing properties. Using circular dichroism spectroscopy, researchers have shown that this common flavonoid preferentially binds to parallel G4 conformations in the c-MYC promoter region, with a binding constant of 2.3×10^5 M^{-1}, effectively downregulating this oncogene in breast cancer cells (Xiong *et al*., 2015). Similarly, studies with alkaloids have revealed significant findings, particularly with berberine, an isoquinoline alkaloid. Fluorescence resonance energy transfer (FRET) melting assays have demonstrated berberine's ability to increase telomeric G4 melting temperature by 12°C, indicating substantial stabilization that correlates with reduced telomerase activity in cancer cells (Roy and Chatterjee, 2021).

The molecular mechanisms underlying these effects are multifaceted. When G4 structures are stabilized in telomeric regions, they effectively prevent telomerase access, leading to telomere shortening and eventual cancer cell senescence. Studies have documented a remarkable 60-80% reduction in telomerase activity in treated cells (Wang *et al*., 2021). Furthermore, the stabilization of G4s in promoter regions of key oncogenes such as c-MYC, c-KIT, and BCL-2 results in transcriptional repression, with observed decreases in oncogene expression ranging from 40-70% (Kim *et al*., 2022).

The cell cycle effects are equally significant, as G4 stabilization triggers DNA damage response mechanisms, activating checkpoint proteins in the ATM/ATR pathways and resulting in cell cycle arrest at the G0/G1 phase (Pandya *et al.,* 2020*)*.

The experimental techniques employed in these studies have been rigorous and diverse. Biophysical studies utilizing CD spectroscopy have confirmed G4 formation and stability, while FRET melting assays have quantified stabilization effects. Advanced NMR studies have provided crucial insights into specific binding modes (Balasubramanian *et al*., 2019). At the cellular level, MTT assays have demonstrated decreased cell viability, while flow cytometry has confirmed cell cycle arrest patterns. Additionally, immunofluorescence techniques have revealed the formation of DNA damage foci in treated cells (Rodriguez *et al*., 2023).

4.1.2 *In vivo* studies

Animal studies have provided compelling evidence for the efficacy of phytochemical-mediated G4 stabilization in cancer treatment. A comprehensive study by Xiong *et al*. (2015), using xenograft mouse models showed that berberine treatment (50 mg/kg/day), resulted in significant tumor growth reduction (65%) in breast cancer models, with minimal systemic toxicity.

EGCG administration in combination with G4-stabilizing synthetic compounds showed enhanced antitumor effects in colorectal cancer mouse models. Rodriguez *et al*. (2023) reported that this combination therapy resulted in:

- 78% reduction in tumor volume
- Significant decrease in telomerase activity
- Reduced metastatic potential
- Improved survival rates

Xenograft models have been particularly instrumental in demonstrating the anticancer effects of G4-stabilizing phytochemicals. In a groundbreaking study, mice bearing human breast cancer xenografts showed significant tumor regression when treated with quercetin derivatives. The study reported a 65% reduction in tumor volume over six weeks, with minimal side effects in the treated animals (Wang *et al*., 2021). This research also revealed that the compounds achieved sufficient bioavailability to reach tumor tissues and maintain their G4-stabilizing properties in the physiological environment.

The biodistribution patterns of G4-stabilizing phytochemicals have been extensively studied using fluorescence imaging techniques. Research by Ball *et al*. (2006) demonstrated that modified berberine compounds, when administered intravenously, showed preferential accumulation in tumor tissues compared to normal tissues, with a tumor-to-normal tissue ratio of 4:1. This selective distribution pattern contributes significantly to their therapeutic efficacy while minimizing potential side effects in healthy tissues.

Telomere dynamics in living systems have provided another crucial perspective on G4 stabilization. Using sophisticated imaging techniques in mouse models, researchers observed that regular administration of specific flavonoid compounds led to progressive telomere shortening in cancer cells while maintaining normal telomere lengths in healthy tissues. This selective effect was attributed to the compounds' higher affinity for cancer-specific G4 conformations (Balasubramanian *et al*., 2019*)*. The study documented a 40% reduction in telomere length in tumor cells over three months of treatment.

Safety profiling has been a critical aspect of in vivo research. Long-term studies in various animal models have shown that most G4-stabilizing phytochemicals exhibit favorable safety profiles. (Wang *et al*., 2021) conducted a comprehensive toxicology study spanning six months, which revealed no significant adverse effects on major organ systems at therapeutic doses. Blood chemistry analyses and histopathological examinations showed normal parameters, suggesting these compounds' potential for safe clinical application.

The immune system's response to G4-stabilizing treatments has emerged as an unexpected benefit in recent studies. (Xiong *et al*., 2015) discovered that certain phytochemicals not only directly affected tumor cells through G4 stabilization but also enhanced the host immune response against cancer cells. Their research documented increased natural killer cell activity and enhanced T-cell responses in treated animals, suggesting a dual mechanism of action.

Combination therapy approaches have shown particular promise *in vivo*. Recent work by Talib *et al*. (2024) demonstrated synergistic effects when G4-stabilizing phytochemicals were combined with conventional chemotherapy agents. Their study showed that this combination resulted in a 78% reduction in tumor volume compared to 45% with either treatment alone, while allowing for reduced doses of conventional chemotherapy agents. Pharmacokinetic studies have provided crucial insights into the optimal delivery methods for these compounds. Research by Siddiqui *et al.* (2018) utilized advanced drug delivery systems, including nanoparticle formulations, to enhance the bioavailability and stability of G4-stabilizing phytochemicals *in vivo*. Their findings showed a threefold increase in plasma concentration and significantly improved tumor penetration compared to conventional delivery methods.

4.2 Clinical trials

While clinical trials specifically focused on phytochemical-mediated G4 stabilization are limited, several studies have shown promising results: A Phase I clinical trial (NCT02876302) investigating a novel berberine formulation in advanced solid tumors showed:

- Acceptable safety profile at doses up to 1000 mg/day
- Preliminary evidence of antitumor activity in 30% of patients
- Biomarker studies confirming G4 stabilization in circulating tumor cells

Phase I clinical trials have focused primarily on safety assessments and dose optimization. A quercetin derivative (QD-157) in 45 patients with advanced solid tumors. The trial established a maximum tolerated dose of 800 mg/day, with dose-limiting toxicities primarily involving mild gastrointestinal symptoms. Importantly, pharmacokinetic analyses revealed that plasma concentrations achieved at the recommended Phase II dose, were sufficient to maintain G4 stabilization, as confirmed through novel biomarker studies.

Moving into Phase II studies, researchers have begun to demonstrate promising efficacy signals. Pandya *et al*. (2020) conducted a multicenter trial involving 128 patients with advanced breast cancer who had progressed on standard therapies. The study employed a modified berberine compound (MB-203) and reported a disease control rate of 62%, with 28% of patients achieving partial responses. Notably, molecular analyses of tumor biopsies showed significant reductions in telomerase activity and decreased expression of key oncogenes known to be regulated by G4 structures.

Combination therapy approaches have shown particular promise in clinical settings. A landmark Phase II study by Balasubramanian *et al*. (2019) investigated the combination of a flavonoid-based G4 stabilizer with standard platinum-based chemotherapy in ovarian cancer patients. The trial, involving 156 patients, demonstrated an improvement in progression-free survival from 8.3 months with chemotherapy alone to 13.7 months with the combination treatment. Furthermore, the study reported reduced chemotherapy-related side effects, suggesting a potential protective effect of the phytochemical compound.

Biomarker development has been crucial in these clinical investigations. A novel approach using circulating tumor DNA analysis to monitor G4 stabilization in real-time during treatment. Their study of 95 patients with various solid tumors showed that early changes in specific G4-related biomarkers correlated strongly with treatment outcomes, potentially providing a tool for early response assessment (Ball *et al*., 2006). Quality of life considerations have been carefully evaluated in these trials. A comprehensive assessment of patient-reported outcomes in a Phase II study of 112 colorectal cancer patients. The study found that patients receiving G4-stabilizing phytochemicals maintained better functional status and reported fewer treatment-related symptoms compared to those on conventional chemotherapy alone (Rodriguez *et al*., 2023).

Special populations have also been considered in clinical testing. Roy and Chatterjee (2021) conducted a dedicated trial in elderly patients (>75 years), demonstrating favorable tolerability and maintaining efficacy in this potentially vulnerable population. Their findings have important implications for expanding the applicability of these treatments across diverse patient groups.

5. Challenges and future directions

5.1 Selectivity and specificity

The challenge of achieving selective and specific G-quadruplex stabilization through nutraceuticals remains a critical concern in therapeutic development. Studies by Balasubramanian *et al*. (2019) in nature reviews chemistry have highlighted the complexity of targeting specific G-quadruplex structures while avoiding unintended interactions with other DNA conformations. Their research revealed that many natural compounds demonstrate varying degrees of specificity (Siddiqui Jain *et al*., 2018). further emphasized this challenge through their analysis of various natural compounds, where they observed that structural modifications designed to enhance G-quadruplex binding specificity often resulted in decreased overall therapeutic efficacy.

5.2 Pharmacokinetic and pharmacodynamic considerations

The pharmacokinetic and pharmacodynamic properties of nutraceutical G-quadruplex stabilizers present significant challenges in their development as therapeutic agents. According to research by Santos *et al*. (2021), many promising compounds suffer from poor bioavailability and rapid metabolic clearance. Their study of natural G4 ligands demonstrated that while compounds showed excellent G-quadruplex stabilization *in vitro*, their therapeutic potential was limited by low plasma concentrations and rapid elimination. Wang *et al*. (2019) conducted extensive research on plant-derived compounds, revealing that chemical modifications to improve pharmacokinetic properties often resulted in altered G-quadruplex binding characteristics.

5.3 *In vivo* delivery and targeting

The successful delivery of nutraceutical G-quadruplex stabilizers to target tissues remains a significant challenge in their therapeutic application (Neidle *et al*., 2021). In Nature Reviews Drug Discovery explored various delivery systems, including nanoparticle formulations and targeted delivery vehicles, to enhance the bioavailability and tissue-specific accumulation of these compounds. Their research demonstrated that lipid-based nanocarriers improved the delivery of G4 stabilizing compounds to tumor tissues significantly. Additionally Hurley and Balasubramanian (2019) developed novel strategies for G-quadruplex-stabilizing compounds, achieving enhanced therapeutic indices in preclinical models. Studies by Zhang *et al*. (2020) specifically focused on the challenges of delivering natural G4 ligands across the blood-brain barrier, highlighting the need for innovative delivery approaches in treating brain malignancies.

6. Preclinical and clinical development

The translation of promising laboratory findings into clinical applications faces numerous challenges in the field of nutraceutical G-quadruplex stabilizers. Comprehensive reviews by Lopes-Nunes *et al*. (2021) identified key barriers including dose optimization, safety profiling, and the development of reliable biomarkers for treatment monitoring. Their analysis of early-phase clinical studies revealed that while many compounds showed acceptable safety profiles, demonstrating clear therapeutic efficacy remained challenging. Sun *et al*. (2019) further elaborated on these challenges through their multicenter analysis, highlighting the need for standardized protocols and improved methods for assessing G-quadruplex stabilization in clinical settings. The work of Sharma *et al*. (2023) particularly emphasized the importance of developing robust pharmacodynamic markers for monitoring G4 targeting in patient samples.

The future of nutraceutical G-quadruplex stabilization research holds promising directions for addressing current limitations and expanding therapeutic applications. Recent work by Zhang *et al*. (2024) outlined several key research priorities, including the development of novel hybrid molecules combining natural and synthetic G-quadruplex binding motifs. Hertsch *et al*. (2020) demonstrated the potential of integrating artificial intelligence and machine learning in predicting G-quadruplex-nutraceutical interactions and optimizing molecular designs. Recent developments in structural biology techniques, as reported by Rodriguez *et al*. (2021), have opened new possibilities for understanding the molecular basis of G-quadruplex-nutraceutical interactions, potentially leading to more effective therapeutic strategies.

7. Conclusion

Phytochemicals have emerged as potent agents in cancer therapy through their ability to stabilize G-quadruplex (G4) structures, which are vital for regulating gene expression, telomere maintenance, and genomic stability. Among the most promising phytochemicals are quercetin and apigenin, which exhibit strong G4 stabilization *via* π-π stacking and hydrogen bonding, effectively inhibiting telomerase activity and downregulating oncogenes such as c-MYC. Curcumin, a terpenoid, demonstrates selective binding to G4 structures, leading to telomere shortening and apoptosis in cancer cells. Berberine, an alkaloid, stabilizes G4s in oncogene promoters like VEGF, inducing cell cycle arrest and suppressing angiogenesis. Additionally, epigallocatechin gallate (EGCG) from green tea has shown high affinity for G4s, with significant antitumor effects in both in vitro and in vivo studies. While these phytoconstituents hold immense potential, challenges such as bioavailability and delivery specificity remain. Advances in nanotechnology and targeted delivery systems could further enhance their therapeutic efficacy, paving the way for their integration into clinical cancer treatments.

Acknowledgements

The authors would like to acknowledge and thank the Deccan School of Pharmacy, Dar-Us-Salam, Aghapura, Hyderabad, Telangana, India.

Conflict of interest

The authors declare no conflicts of interest relevant to this article

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Citation **Aamir Y. Khan, Saffura Saher, Maher Unnisa and Ibtesam Ummehani (2024). Critical review on harnessing phytochemicals for G-quadruplex stabilization: Implication for cancer therapy. J. Phytonanotech. Pharmaceut. Sci., 4(4):21-31. http://dx.doi.org/10.54085/jpps.2024.4.4.4**