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(REVIEW ARTICLE)

Strategic improvement of bioavailability in flavonoids by using non - oral routes

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Abstract

Flavonoids are polyphenolic chemicals that exist naturally and are well known for their strong anti-inflammatory, anti-oxidant, and medicinal properties. However, significant first-pass hepatic metabolism, enzymatic breakdown in the gastrointestinal system, and poor oral bioavailability resulting from low water solubility frequently restrict their clinical usefulness. Transdermal, intranasal, buccal, pulmonary, and rectal drug delivery methods have become viable substitutes to get around these restrictions. These pathways improve systemic absorption and therapeutic efficacy by avoiding hepatic metabolism and gastrointestinal breakdown. More sophisticated drug delivery methods, such as liposomes, microneedles, nanocarriers, and mucoadhesive formulations, help to enhance the permeability, sustained release, and targeted administration of flavonoids. The strategic use of non-oral methods and innovative formulations to improve flavonoid bioavailability is highlighted in this article, opening the door to more efficient and patient-friendly treatment alternatives.

Keywords: Flavonoids; Bioavailability; First Pass Metabolism; Permeability; Non-Oral Routes

1. Introduction to flavonoids

Flavonoids-A broad class of naturally occurring polyphenolic chemicals that are widely distributed throughout the plant kingdom are called flavonoids. They are secondary metabolites that are vital to plants' defence against UV rays, diseases, and herbivores(1). They are mainly responsible for the vibrant colouring found in flowers, fruits, and leaves. The C6-C3-C6 skeleton, which is the structural backbone of flavonoids, is made up of two aromatic rings (A and B) connected by a three-carbon bridge to produce an oxygen-containing heterocyclic ring (C)(2). A significant class of secondary metabolites, flavonoids are abundantly present in fruits, vegetables, herbs, stems, cereals, nuts, flowers, and seeds. The number of isolated and recognized flavonoid compounds to date exceeds 10,000. Plant flavonoids are significant secondary metabolites that control pollination, auxin transport, male fertility, seed development, flower colour, and allelopathy(3). Against biotic (bacteria, fungus, herbivores) and abiotic (ultraviolet radiation, cold, salt, drought, and heavy metals) stressors, flavonoids provide protection. Depending on their degree of unsaturation, oxidation of the carbon ring, and chemical structure, flavonoids are divided into many categories, such as- The six main classes include:

- Flavanols (e.g., quercetin, kaempferol)
- Flavones (e.g., luteolin, apigenin)
- Flavanones (e.g., naringenin, hesperetin)
- Flavan-3-ols (flavanols) (e.g., catechins, epicatechin)
- Anthocyanins (e.g., cyanidin, delphinidin)
- Isoflavones (e.g., genistein, daidzein).

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All these flavonoids are found in large quantities in nature. Each class of flavonoids has their own significance in both the plants and human beings. Beneficial biochemical and antioxidant effects of flavonoids have been observed in several disorders, including cancer, neurological disease, and cardiovascular disease. A wide range of health-promoting benefits are linked to flavonoids, which are also essential ingredients in many pharmacological, cosmetic, nutraceutical, and medical uses. Their ability to control the operation of important cellular enzymes and their anti-inflammatory, anti-oxidative, anti-carcinogenic, and anti-mutagenic qualities are primarily responsible for this(1).

The limited oral bioavailability of flavonoids is a significant barrier to their clinical use, despite their potential for therapeutic benefit. Rapid elimination, extensive gastrointestinal metabolism, and low water solubility are among of the factors that lead to poor bioavailability. To improve their systemic availability and therapeutic efficacy, other approaches—such as innovative formulations and non-oral delivery routes—are being investigated in recent years(2)

1.1. Challenges in Oral Delivery of Flavonoids

Even though flavonoids are widely available in food and have many therapeutic benefits, pharmacokinetic restrictions that impact their absorption, metabolism, distribution, and bioavailability make it extremely difficult to provide them orally. The challenges include –

1.1.1. Poor water solubility

- Low permeability & efflux transport
- Extensive first pass metabolism
- Instability in gastrointestinal tract
- Interaction with gut microbiota
- Low bioavailability
- Dose escalation not a solution

1.1.2. Poor water solubility

The low aqueous solubility and high lipophilic nature of many flavonoids limit their ability to dissolve in gastrointestinal (GI) fluids, which is necessary for absorption via the intestinal epithelium(3)(4). Flavonoids are polyphenolic chemicals that have a rigid planar structure because they include hydroxyl groups and many aromatic rings(5). Despite having hydrophilic -OH groups, many flavonoids are just partially soluble in water due to the dominance of lengthy hydrophobic regions and complex conjugated systems(6). For example: The water solubility of quercetin is around 2 μg/mL, which restricts its absorption in the small intestine.

1.1.3. Low permeability and efflux transport

Low intestinal permeability and active efflux transport systems, in addition to poor water solubility, are major obstacles to the effective absorption of flavonoids. Since flavonoids have rigid planar structures, strong polarity from many hydroxyl groups, and large molecular sizes that limit their transcellular transit, they exhibit limited passive diffusion across the intestinal epithelium despite their lipophilic properties. More importantly, ATP-binding cassette (ABC) efflux transporters, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP/ABCG2), and multidrug resistance-associated proteins (MRPs) on the apical side of enterocytes, are known to bind flavonoids as substrates. In order to decrease the net absorption and systemic availability of absorbed flavonoids, these transporters actively pump them back into the intestinal lumen. For example, it is well known that P-gp and BCRP widely efflux quercetin and kaempferol, which significantly reduces their intracellular retention and subsequent absorption. Low and irregular plasma concentrations are the outcome of this process, which also adds to the substantial interindividual variability frequently observed in flavonoid pharmacokinetics. The prediction of flavonoid bioavailability is further complicated by the fact that these efflux pathways are saturable, energy-dependent, and susceptible to modification by genetic polymorphisms, illness conditions, and nutrition. Innovative approaches including the use of efflux pump inhibitors, nanocarrier systems that can avoid efflux recognition, or non-oral delivery methods that completely avoid the intestinal barrier are needed to overcome these transport-related hurdles.

1.1.4. Extensive first pass metabolism

Flavonoids' considerable first-pass metabolism, which significantly lowers their systemic bioavailability, is another important drawback when it comes to oral administration(7). The gastrointestinal tract absorbs flavonoids after consumption, and the portal vein carries them to the liver, where they go through phase I and phase II metabolic changes before entering the bloodstream(8). The parent molecule may be oxidised or hydrolysed by cytochrome P450 enzymes in phase I, whereas flavonoids undergo conjugation processes like glucuronidation, sulfation, and methylation to

become more hydrophilic metabolites in phase II(9). These conjugates may have less biological action than the parent chemical and are frequently quickly eliminated through bile or urine.

1.1.5. Instability in Gastrointestinal tract

The gastrointestinal tract (GIT) is often marked by significant instability in flavonoids, which further hinders their systemic availability and efficient absorption. Digestive enzymes, bile salts, the stomach's acidic pH, and the microbiota are some of the harsh and fluctuating conditions of the gastrointestinal tract (GIT) that can cause flavonoids to undergo structural or chemical changes prior to absorption(10). For example, a lot of flavonoids are sensitive to pH and become unstable in the stomach's acidic environment. They can undergo isomerisation, oxidation, or hydrolysis. Furthermore, digestive enzymes such β-glucosidases break down the glycosidic linkages in flavonoid glycosides in the small intestine, occasionally producing less soluble or more amenable to further breakdown aglycones(11).

1.1.6. Interaction with gut microbiota

The bioavailability, metabolism, and biological activity of flavonoids are significantly influenced by their extensive and complementary interactions with the gut microbiota. Only a small portion of flavonoids are absorbed in the upper gastrointestinal tract after oral consumption; the majority enter the colon and encounter the rich microbial environment there. Numerous enzymes found in gut bacteria, including as glycosidases, reductases, and decarboxylases, can convert flavonoids into a variety of low-molecular-weight metabolites that are frequently more accessible and bioactive than the original substances. Quercetin, rutin, and daidzein, for example, are broken down into smaller phenolic acids or bioactive substances like 3,4-dihydroxyphenylacetic acid and equol, which have anti-inflammatory, antioxidant, and even neuroprotective properties(12). By suppressing harmful bacteria and promoting the growth of favourable microorganisms like Lactobacillus and Bifidobacterium species, flavonoids can simultaneously alter the composition and activity of the gut microbiota. Their systemic advantages, particularly in instances like obesity, metabolic syndrome, and inflammatory bowel disease, may be attributed to this prebiotic-type effect. However, the metabolic destiny and subsequent bioactivity of flavonoids are extremely individual-dependent and controlled by dietary, age, health, genetic, and microbial diversity and functional capacity. Thus, the gut microbiota is an important consideration in flavonoid-based therapy strategies since it not only serves as a metabolic gatekeeper for flavonoids but also influences inter-individual variability in their pharmacological response(13).

1.1.7. Low bioavailability

Although flavonoids have a wide range of pharmacological potential, their therapeutic value is greatly restricted by their extremely low oral bioavailability. The term "bioavailability" describes the percentage of a dose that enters the bloodstream in an active state. For many flavonoids, this percentage is incredibly low, frequently less than 10%. A mix of biological and physical obstacles contribute to this low bioavailability(14). First off, a lot of flavonoids are poorly soluble in water, which prevents them from dissolving in digestive juices, which is necessary for absorption. Second, flavonoids' large molecular size and hydrophilic nature—particularly in glycoside forms—often result in reduced permeability across intestinal epithelium. Furthermore, flavonoids undergo conjugation events such glucuronidation, sulfation, and methylation in the intestinal wall and liver, where they undergo substantial first-pass metabolism even if they are absorbed. The therapeutic potential of the active chemicals may be diminished by these processes, which can cause their rapid transformation and elimination. In addition, flavonoids are actively pumped back into the intestinal lumen by efflux transporters such as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which further reduces systemic absorption. Following oral treatment, the combined action of these obstacles results in a low and very fluctuating plasma concentration of the active flavonoid. To find ways to go around or beyond these limitations, novel formulation techniques, bioenhancers, and alternative non-oral administration methods are being used in current research to address the problem of limited bioavailability.(15)

1.1.8. Dose escalation not a solution

Dose escalation seems like a straightforward way for flavonoids' poor bioavailability, but in most situations, it is neither practical nor efficient. Due to the saturation of intestinal transport systems, enzymatic routes, and efflux transporters like P-glycoprotein and BCRP, increasing the oral dose does not correspondingly increase systemic exposure. Additionally, flavonoids frequently have non-linear pharmacokinetics, which means that at a certain point, higher dosages of the active ingredient result in little to no rise in plasma concentrations. In instance, flavonoids that are poorly absorbed and stay in the gut lumen can cause undesirable gastrointestinal side effects as nausea, bloating, or diarrhoea when consumed in high concentrations. Their therapeutic value may be decreased in certain cases by excessive local concentrations, which can even have pro-oxidant effects instead of antioxidant ones. Furthermore, no matter how much is taken, the first-pass metabolism in the liver and intestine may continue to operate as a bottleneck, turning most of the flavonoid intake into metabolites that are either inactive or quickly eliminated. Consequently, increasing the dosage

alone is ineffective and may cause safety issues. Instead, more focused and sensible methods for enhancing flavonoid bioavailability without raising the risk of toxicity are provided by novel techniques such non-oral delivery methods, co-administration with bioenhancers, and nano formulations.

2. Non-oral routes to enhance the bioavailability of flavonoids

2.1. Transdermal delivery

For flavonoids, transdermal drug delivery presents a strong alternative for oral administration, mainly because it can prevent gastrointestinal degradation, hepatic first-pass metabolism, and maintain systemic drug levels. But for transdermal administration to be effective, the stratum corneum—the skin's outermost layer—must be overcome. This layer acts as a significant barrier for medication penetration. Flavonoids are difficult to absorb directly via the skin since they are hydrophilic, poorly permeable, and chemically unstable by nature. Therefore, to enable efficient distribution, novel formulation techniques are required. Drugs can enter the systemic circulation through the epidermis and dermis using transdermal devices, either for localised or systemic effects. The main advantage of transdermal delivery over oral route of administration is – it avoids gastrointestinal degradation, provides controlled and prolonged release, also enhances the patient compliance.

2.2. Pulmonary delivery

A potential non-oral method for increasing the bioavailability of flavonoids, particularly for treating respiratory conditions and producing quick systemic effects, is pulmonary administration. Efficient absorption of inhaled chemicals is made possible by the lungs' enormous surface area, dense capillary network, and thin alveolar membranes. Bypassing the gastrointestinal tract and hepatic first-pass metabolism, this method increases the systemic availability of flavonoids, which are otherwise restricted by their low solubility and enzymatic breakdown in the gut. When given via pulmonary formulations such as solid lipid nanoparticles, liposomes, nano emulsions, and dry powder inhalers, flavonoids like quercetin, naringenin, and baicalein have shown notable therapeutic advantages. These innovative delivery methods allow for regulated release at the site of action, enhance flavonoid solubility, and shield them from oxidative destruction. Because flavonoids have potent antioxidant, anti-inflammatory, and anti-fibrotic qualities, pulmonary administration is especially beneficial for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. This method also guarantees low systemic side effects and a quick beginning of action. All things considered, pulmonary administration provides a focused, effective, and non-invasive way to increase the therapeutic potential of flavonoids.

2.3. Intranasal delivery

For improving the bioavailability of flavonoids, especially those targeted to the central nervous system (CNS), intranasal delivery presents a viable non-oral option. Via the olfactory and trigeminal nerves, the nasal mucosa facilitates direct nose-to-brain transfer and quick systemic absorption because to its rich vascular network and highly permeable epithelial membrane. Flavonoids with poor oral absorption and gut instability benefit from this pathway since it avoids the gastrointestinal tract and hepatic first-pass metabolism. Flavonoids like rutin, hesperetin, and baicalein have been investigated in intranasal formulations such as solid lipid nanoparticles, in situ gels, and nano emulsions. These cutting-edge carriers boost brain absorption, shield flavonoids from enzymatic degradation, and strengthen mucosal adherence. Because flavonoids have neuroprotective, antioxidant, and anti-inflammatory qualities, intranasal administration has demonstrated promise in the treatment of neurodegenerative illnesses including Parkinson's and Alzheimer's. Additionally, this method guarantees a non-invasive, bypasses first pass metabolism, quick-onset, and patient-friendly substitute for oral or intravenous delivery of CNS-active flavonoids.

2.4. Buccal and sublingual delivery

By circumventing the drawbacks of oral administration, encompassing gastrointestinal tract enzymatic degradation and substantial first-pass hepatic metabolism, buccal and sublingual methods are effective alternatives to enhance the bioavailability of flavonoids. Because of the strong vascularization of the oral mucosa, medications can be quickly absorbed and delivered directly into the bloodstream (16). Particularly when administered sublingually, the thin epithelial layer and abundant blood flow beneath the tongue allow for a quicker beginning of effect. Despite being a little slower, buccal administration allows for extended retention times and sustained release, which makes it appropriate for long-lasting therapeutic effects (17). Multiple research studies have shown how effective these methods are at delivering flavonoids such as rutin, quercetin, and naringenin (18). For example, flavonoids with nanocarriers such liposomes or solid lipid nanoparticles have demonstrated improved solubility, permeability, and mucosal residence duration in bioadhesive buccal films and sublingual tablets. Furthermore, mucoadhesive devices can offer controlled

release and prevent flavonoids from enzymatic breakdown (19). These methods greatly enhance flavonoids' pharmacokinetic profile, which increases their therapeutic efficiency in treating diseases like cardiovascular disorders, oxidative stress, and inflammation (20).

2.5. Parenteral route: (IM, IV, SC)

Flavonoids can be directly delivered into the systemic circulation through parenteral administration, which includes intravenous (IV), intramuscular (IM), and subcutaneous (SC) methods. This method avoids the gastrointestinal tract and first-pass hepatic metabolism. Flavonoids with low water solubility, restricted permeability, and instability in the acidic Gastric environment benefit most from this approach. For acute diseases or situations where a therapeutic effect is immediately needed, parenteral delivery is the best option since it guarantees a quick onset of action, great bioavailability, and optimal control over plasma drug levels. But because most flavonoids are hydrophobic, using them parenterally often requires encapsulation in drug delivery systems such nanoparticles, liposomes, dendrimers, or polymeric micelles, or formulation with solubilising agents. For example, polymeric nanoparticles loaded with quercetin have been effectively injected, showing increased anticancer activity, prolonged circulation time, and better absorption. Similarly, in an inflammatory approach, parenteral nanocarriers of another flavonoid, baicalin, have demonstrated enhanced therapeutic activity. In situations where oral and other non-invasive methods are inefficient or unfeasible, parenteral distribution is still a viable alternative for improving the clinical performance of flavonoids, despite its invasiveness and risk for injection site problems.

3. Pharmacological actions of flavonoids

Flavonoids are a diverse group of naturally occurring polyphenolic compounds abundantly present in fruits, vegetables, and medicinal plants. Their extensive pharmacological activities contribute significantly to their therapeutic potential across various pathological conditions. One of the most prominent features of flavonoids is their antioxidant activity, which is primarily mediated through free radical scavenging, metal ion chelation, and the upregulation of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) (21). This antioxidant property plays a crucial role in preventing oxidative stress-related cellular damage. Flavonoids also exhibit potent anti-inflammatory effects by modulating key signalling pathways including nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and cyclooxygenase-2 (COX-2). These interactions result in the downregulation of pro-inflammatory cytokines and mediators, thereby attenuating inflammatory responses (22). Their anticancer activities are mediated through the regulation of molecular targets such as p53, PI3K/Akt, and Bcl-2, leading to inhibited cell proliferation, induced apoptosis, suppression of angiogenesis, and inhibition of tumor metastasis (23). Flavonoids have also shown promise in metabolic disorders by improving insulin sensitivity, modulating glucose uptake, and regulating lipid metabolism, thereby exhibiting antidiabetic and antihyperlipidemic effects (24). Their neuroprotective potential involves antioxidant, anti-inflammatory, and anti-amyloidogenic mechanisms, which enhance cognitive functions and mitigate neuronal damage in neurodegenerative diseases such as Alzheimer's disease (25). In addition, many flavonoids possess antimicrobial (antibacterial and antiviral), hepatoprotective, and immunomodulatory properties, further expanding their applicability in clinical and therapeutic settings (26).

3.1. Antioxidant activity

One of the most important pharmacological characteristics of flavonoids is their strong antioxidant activity, which helps to protect biological systems from oxidative stress by neutralising reactive oxygen species (ROS) like superoxide anions, hydroxyl radicals, and hydrogen peroxide. Their polyphenolic structure, in particular the presence of hydroxyl groups and conjugated double bonds, is largely responsible for this ability to scavenge free radicals by donating hydrogen atoms or electrons to stabilise them. In addition to direct scavenging, flavonoids chelate redox-active metal ions like iron and copper, which stops ROS formation through Fenton and Haber-Weiss reactions. Furthermore, through activating the Nrf2 signalling pathway, flavonoids suppress oxidative enzymes like xanthine oxidase and NADPH oxidase and regulate the expression of antioxidant defence enzymes including glutathione peroxidase, catalase, and superoxide dismutase (SOD). The presence and arrangement of hydroxyl groups, particularly in the B-ring, the C2-C3 double bond, and the 4-oxo function in the C-ring, structurally affect the antioxidant capability of flavonoids. Flavonoids with potent antioxidant properties, such as quercetin, catechin, and epigallocatechin gallate (EGCG), have been extensively researched. Flavonoids support overall cellular health, shield biomolecules from oxidative damage, and preserve redox equilibrium through these complex processes.

3.2. Anti-inflammatory activity

Flavonoids are promising medicinal products in the prevention and treatment of a variety of inflammatory and autoimmune diseases because of their strong anti-inflammatory properties. They have anti-inflammatory properties

through a variety of molecular mechanisms that control the production and function of pro-inflammatory mediators. Flavonoids suppress the expression of enzymes that produce inflammatory substances such prostaglandins, leukotrienes, and nitric oxide (NO), including cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS). They also prevent important transcription factors from being activated, especially nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), which are important modulators of the production of cytokine genes. As a result, flavonoids inhibit the release of pro-inflammatory cytokines such interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α). To further enhance their anti-inflammatory properties, many flavonoids also alter the mitogen-activated protein kinase (MAPK) signalling pathway. For these qualities, flavonoids such as kaempferol, luteolin, apigenin, and quercetin have been thoroughly investigated. Flavonoids have therapeutic potential in illnesses like arthritis, asthma, atherosclerosis, and inflammatory bowel disease because of their ability to reduce both acute and chronic inflammation through these processes.

3.3. Neuroprotective effects

Flavonoids exhibit strong neuroprotective properties that have garnered significant interest due to their potential to prevent and treat neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and stroke-related brain injury. These polyphenolic compounds work through a variety of mechanisms, but mainly by reducing oxidative stress and neuroinflammation, which are major causes of neuronal damage. Flavonoids easily pass through the blood-brain barrier and act as antioxidants by scavenging reactive oxygen species (ROS), chelating neurotoxic metal ions, and upregulating endogenous antioxidant enzymes through the Nrf2 signalling pathway. In addition to their antioxidant properties, flavonoids also prevent the activation of microglia, which helps lower the release of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. Additionally, flavonoids enhance the expression of brain-derived neurotrophic factor (BDNF), which is crucial for synaptic plasticity and memory formation, and modulate important signalling pathways involved in neuronal survival, such as the PI3K/Akt and MAPK/ERK pathways. Some flavonoids, such as quercetin, epigallocatechin gallate (EGCG), luteolin, and apigenin, have demonstrated promising results in protecting neurones against amyloid-beta toxicity, mitochondrial dysfunction, and excitotoxicity. Through these complex mechanisms, flavonoids promote cognitive function, preserve neural integrity, and slow the progression of neurodegenerative diseases.

3.4. Cardioprotective effects

Atherosclerosis, hypertension, myocardial infarction, and stroke are among the cardiovascular diseases (CVDs) that flavonoids are useful in preventing and treating because of their strong cardioprotective properties. They mainly use lipid-lowering, anti-inflammatory, antioxidant, and vasodilatory pathways to mediate their protective effects. By scavenging free radicals and boosting the activity of antioxidant enzymes like glutathione peroxidase and superoxide dismutase, flavonoids help prevent oxidative alteration of low-density lipoprotein (LDL), a crucial stage in the development of atherosclerosis. Additionally, by boosting nitric oxide (NO) bioavailability, which encourages vasodilation and enhances vascular tone, they prevent endothelial dysfunction. Furthermore, flavonoids limit leukocyte infiltration and plaque formation by suppressing inflammatory processes in blood vessels by lowering the expression of adhesion molecules (such as VCAM-1 and ICAM-1) and blocking NF-κB activation. It has been demonstrated that several flavonoids, including quercetin, epicatechin, and kaempferol, lower blood pressure, prevent platelet aggregation, and enhance lipid profiles by raising HDL and decreasing total cholesterol and triglyceride levels. Flavonoids are prospective nutraceuticals or adjuvants in cardiovascular therapy because of their diverse activities, which improve endothelial function, lower vascular inflammation, and improve cardiac performance.

4. Conclusion

Flavonoids' extensive metabolism and low oral absorption make increasing their bioavailability a major hurdle in pharmaceutical research. By avoiding the gastrointestinal system and first-pass metabolism, non-oral administration methods present a viable way to enhance systemic availability and therapeutic results. When paired with cutting-edge delivery methods including nanocarriers, microneedles, and mucoadhesive formulations, transdermal, intranasal, buccal, pulmonary, and rectal routes have shown great promise in overcoming the intrinsic drawbacks of flavonoids.

In addition to improving absorption and bioavailability, these tactics allow for tailored and long-term medication delivery. Translating flavonoid-based medicines into clinically viable and patient-friendly therapy alternatives requires ongoing research and improvement of these strategies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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