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Therapeutic aspects of genistein based on recent advances and challenges

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ABSTRACT

The most promising avenues for improving conventional drugs are those based on biocompatible organic compounds. These bioactive compounds can be isolated from natural sources such as plants, fungi, bacteria, and lichens. Genistein is an isoflavone naturally isolating from legumes of medicinal plant species. This phytoestrogen is structurally similar to mammalian estrogens. Several therapeutic effects including anticancer, antibacterial, antioxidant, antidiabetic, and anti-neurodegenerative activities have been indicated for genistein and plants containing this metabolite. Low aqueous solubility and bioavailability are the main limitations for clinical applications of this compound. In this way, in recent years, new micro and nanoformulations have been presented to overcome these limitations. Here, we have tried to focus on the efficiency of micro and nanoformulations of genistein for anticancer, antioxidant, antimicrobial, antidiabetic, and anti-neurodegenerative aspects.

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Introduction

Genistein ($C_{15}H_{10}O_5$) is an isoflavone naturally isolating from *Flemingia vestita* [1], *F. macrophylla* [2], and *Lupinus albus* (Figure 1) [3]. This metabolite is structurally similar to mammalian estrogens and mainly derived from legumes of medicinal plant species [4]. Several molecular functions have been found for genistein such as agonist of G protein-coupled estrogen receptor [5], inhibition of tyrosine kinases [6], inhibition of topoisomerase II [7], activation of peroxisome proliferator-activated receptors (PPARs) [8], activation of Nrf2 antioxidative response stimulation of autophagy [9], inhibition of the mammalian hexose transporter GLUT1 [10], inhibition of cytosine methylation inhibition of DNA methyltransferase [11], inhibition of the glycine receptor [12], inhibition of IL-6/IL-6R interface of the Interleukin-6–mediated STAT3 pathway [13], and inhibition of the nicotinic acetylcholine receptor [14]. In addition, anticancer [15], antioxidant [16], antidiabetic [17], antimicrobial [18], and neuroprotective [19] activities have been reported as the main medical properties of genistein. A synergistic effect is expected for the genistein combination therapy compared to a single component [20]. Moreover, a variety of nanoformulations of this phytocompound by synthetic and organic nanomaterials may ameliorate its bioavailability [21-24]. In this review, we have tried to focus on the efficiency of micro and nanoformulations of genistein for anticancer, antioxidant, antimicrobial, antidiabetic, and antineurodegenerative aspects.

Anticancer activity

The major anticancer actions of genistein have been illustrated in Figure 2. Genistein can inhibit the functions of receptor tyrosine kinase such as cyclin-dependent kinase 1 (CDK1) and polo-like kinase 1 (PLK1). In addition, suppressing the transcriptional expression of PLK1 is modulated by genistein. Moreover, genistein is structurally similar to 17β-estradiol (Figure 3) and can act as a modulator of hormone receptors [25]. The applications of organic

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and inorganic nanomaterials for loading and incorporation of therapeutic agents such as genistein are increasing because unique physicochemical properties of these nanomaterials compared to bulk materials [26-28]. For example, biodegradable polymers such as poly(lactic-co-glycolic-acid) (PLGA) can reduce the burst release of therapeutic agents such as various types of flavonoids. Additionally, a pH-sensitive polymer, Eudragit S100, protects formulations from damage in the stomach and small intestine (Figure 4) [20].

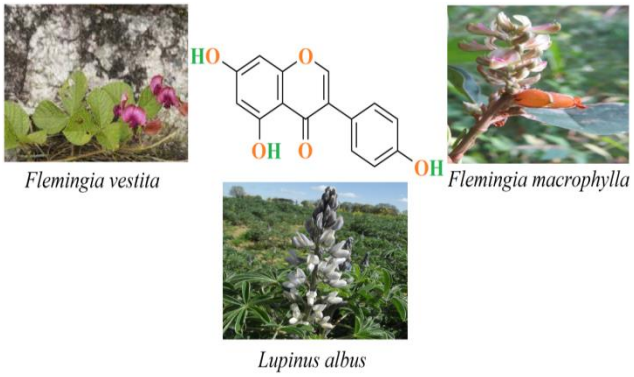

Fig. 1. Chemical structure of genistein with three main plant sources.

Genistein and temozolomide were loaded on PLGA nanoparticles for the improvement of anticancer efficiency against Glioblastoma multiforme. These NPs showed IC_{50} values of 35.2 and 8.7 µg/mL against U87MG human glioblastoma cells after 24 h and 48 h, respectively. The significant anticancer effects of this formulation were decreased cell proliferation, inhibition of cell migration, and induction of intrinsic apoptosis by up-regulation of the mRNA level of apoptotic genes [29]. This type of brain cancer is highly invasive and possesses poor drug penetration and drug resistance because of the diffuse infiltrative growth [30]. Current chemotherapeutic drugs do have not enough efficiency to eradicate metastatic prostate cancer as the second most common malignancy in men. Genistein was loaded on gold (Au) nanoparticles with loading efficiencies of 46% and 48% with hydrodynamic diameters of 65 and 153 nm as well as zeta potential values of −35.0 mV and −37.0 mV, respectively. Nano-conjugate of genistein-AuNPs showed antiproliferative activities against three prostate carcinoma cell lines of LNCaP, PC3, and DU 145. In the case of the LNCaP cell line, IC_{50} values were in the range of 19.6- 29.3 µg/mL compared to pure genistein with the value of 13.9 µg/mL [31].

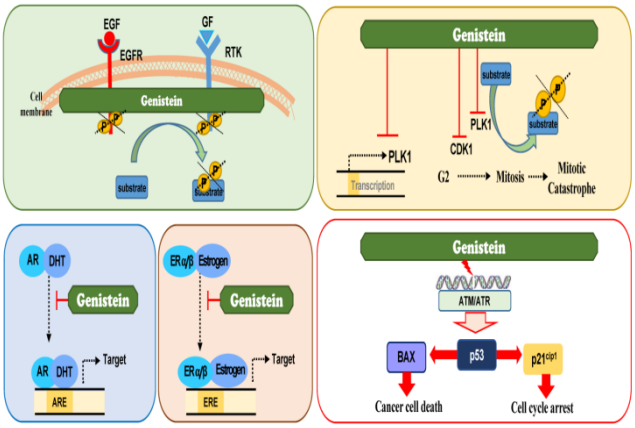

Fig. 2. The main molecular targets of genistein. Growth factor (GF), epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), receptor tyrosine kinase (RTK), cyclin-dependent kinase 1 (CDK1), polo-like kinase 1 (PLK1), androgen receptor (AR), dihydrotestosterone (DHT), estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), Bcl-2-associated X protein (BAX), ataxia-telangiectasia mutated (ATM), ataxia telangiectasia and rad3-related (ATR), cyclin-dependent kinase inhibitor 1 (p21Cip1), and tumor protein p53 (p53) (adopted and modified from [25]).

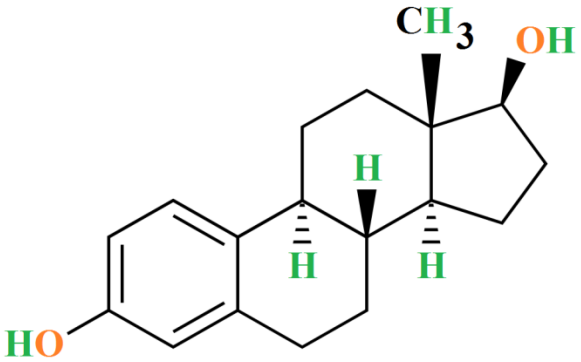

Fig. 3. Chemical structure of 17β-estradiol is similar to genistein.

Antimicrobial activity

Monotherapy and combination therapy of genistein can lead to different antibacterial strengths against Gram-negative and Gram-positive bacteria. Genistein with a concentration of 100 µg/mL in the combined formulation of gentamicin and genistein changed antibiotic-resistant *Acinetobacter baumannii* to susceptible bacteria. Minimum inhibitory concentrations (MICs) for genistein toward *A. baumannii* (PBIO721), *A. baumannii* (PBIO2202), and *A. baumannii* (PBIO2212) were 400 µg/mL [32].

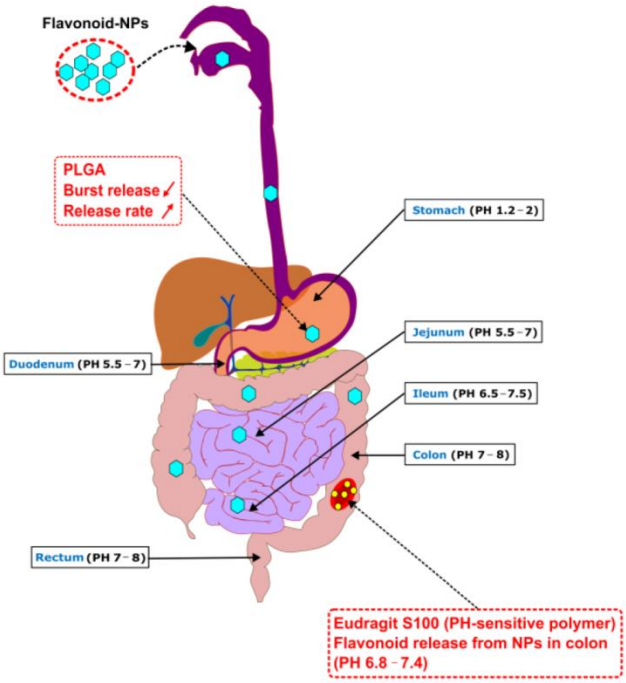

Fig. 4. The application of Eudragit S100, a pH-sensitive polymer for protection of formulations from damage in the stomach and small intestine (extracted and modified from [20]).

Antibacterial activity of ternary formulation composed of the inclusion complex genistein, Hydroxypropyl β cyclodextrin, and poloxamer 188 was tested against *Staphylococcus aureus* and *Bacillus subtilis*. This formulation hindered *B. subtilis* and *S. aureus* by inhibition zone diameters of 9.34 and 11.54 mm, respectively. High internalization of genistein in bacteria resulting from the high solubility of genistein in the inclusion complex was the main antibacterial mechanism for this formulation [33]. Methicillin-resistant *S. aureus* (MRSA) can lead to resistant infections of septicemia, osteomyelitis, pneumonia, endocarditis, otitis media, and food poisoning [34]. In vivo study exhibited that genistein at a dose of 50 mg/kg body weight for administration twice daily for two weeks, remarkably decreased serum pro-inflammatory cytokines, IL-6 (interleukin 6), and TNF-α (tumor necrosis factor-ealpha) and hindered the growth of MRSA associated with osteomyelitis in male Wistar rats [35]. Aerolysin is the main virulence factor produced by an opportunistic pathogen of *Aeromonas hydrophila*. Uncooked aquatic food is the source of these foodborne bacteria causing infections of eczema and myonecrosis [36]. Conventional antibiotics cannot eradicate resistant *A. hydrophila* strains. The biofilm formation and generation of aerolysin of *A. hydrophila* have been inhibited upon genistein treatment in a dose-dependent way [37]. Poloxamer 188 (PL 188) and hydroxypropyl β cyclodextrin (HP β CD) were employed to prepare inclusion complexes of binary (genistein: HP β CD) and ternary (genistein: HP β CD: PL 188). Genistein ternary complex and genistein showed inhibition zone diameters (IZDs) of 17.65 mm and 11.54 mm against *S. aureus*, respectively [33].

Antidiabetic activity

Diabetes is a common and epidemic disease. During the studies conducted by Gilbert et al. in 2013, approximately (8% of the US population) had diabetes, which is expected to double in the next 15 years. Surgical intervention has improved survival rates for people with diabetes, yet the prevalence of diabetes in Americans continues to rise. Diabetes brings an average of $6,000 in medical costs per year, so there is an urgent need to develop strategies such as effective detection to treat this disease. Type 2 diabetes is the result of chronic resistance of cells to insulin and increased blood sugar, which leads to the loss of β cells and decreased pancreatic function. Strategies to prevent and treat this devastating disease are needed to preserve β-cell mass [38]. Physiological indicators in humans have shown that soy consumption is associated with positive outcomes on blood sugar control. Soy is a huge source of phytoestrogen or plant estrogen from which three isoflavones, Gainstein, Daidzein, and Glyctein, are extracted. In general, isoflavones in soybeans include 37% daidzein, 57% genistein, and 6% glycine. Genistein and daidzein have very strong antioxidant properties. Genistein's anti-diabetic effects are mostly related to the cAMP/PKA signaling pathway, so it interferes with insulin signaling by interfering with cAMP accumulation and PKA activation. Liu et al., 2006 showed that genistein-induced cAMP, at physiological concentrations, may primarily result from increased adenylate cyclase activity. Pharmacological, molecular intervention, and PKA activation showed that the insulinotropic effect of genistein is primarily caused by PKA. Genistein also acts directly on pancreatic beta cells, leading to activation of the cAMP/PKA signaling cascade to exert an insulinotropic effect, thus providing a novel role in the regulation of insulin secretion [39]. In general, genistein is effective in controlling diabetes through its direct effect on β-cell proliferation, glucose

stimulation, and insulin secretion. Data from recent animal studies suggest an antidiabetic effect of genistein possibly through a hypolipidemic effect [40]. Also, some studies have shown that genistein focuses on anti-diabetic properties by regulating epigenetics and gene expression. There are a large number of animal and cell culture studies showing that genistein, at physiologically relevant concentrations (<10 μM), has a direct effect on pancreatic β-cells. Diabetes causes complications in general health and increases the risk of premature death. It should be noted that women after natural or surgical menopause are more vulnerable to developing diabetes due to the imbalance or absence of hormones [41]. Absence of ovarian hormones after menopause alters glucose metabolism, resulting in blood sugar fluctuations. There is little information about hormonal changes with impaired glucose metabolism, however, studies have shown that hormonal changes alter glucose metabolism and increase the risk of diabetes. HRT Hormone replacement therapy (HRT) probably has beneficial effects on glucose metabolism; however, some observations have shown a positive correlation with an increased risk of cardiovascular disease. Therefore, its use for diabetes in postmenopausal women is still under investigation. Interestingly, genistein regulates this metabolism and has shown favorable effects [42].

Conclusions

Low water solubility and bioavailability are the main disadvantages of clinical applications of genistein. Significant bacterial growth inhibition and reduction in serum pro-inflammatory cytokines, IL-6, and TNF-α have been indicated for genistein against osteomyelitis in male Wistar rats. Loading and encapsulation of this bioactive compound in micro nano-carriers have been reported in various investigations. This review showed that genistein in combination therapy has a synergistic effect compared to monotherapy.

Study Highlights

- Low water solubility and bioavailability are the main disadvantages of clinical applications of genistein.
- Significant bacterial growth inhibition and reduction in serum pro-inflammatory cytokines, IL-6, and TNF-α have been indicated for genistein.
- Loading and encapsulation of this bioactive compound in micro nano-carriers have been reported in various investigations.

Abbreviations

AR: Androgen receptor
ATM: Ataxia-telangiectasia mutated
ATR: Ataxia telangiectasia and rad3-related
BAX: Bcl-2-associated X protein
CDK1: Cyclin-dependent kinase 1
DHT: Dihydrotestosterone
EGF: Epidermal growth factor
EGFR: Epidermal growth factor receptor
ERα: Estrogen receptor alpha
ERβ: Estrogen receptor beta
GF: Growth factor
HP β CD: Hydroxypropyl β cyclodextrin
IL-6: Interleukin 6
MRSA: Methicillin-resistant *Staphylococcus aureus*
p21Cip1: Cyclin-dependent kinase inhibitor 1
p53: Tumor protein p53
PL 188: Poloxamer 188
PLK1: Polo-like kinase 1
RTK: Receptor tyrosine kinase
TNF-α: Tumor necrosis factor-alpha

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author Contributions

All authors: conceptualization, preparing the first draft, and editing.

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