The Role of Flavonoids in GH and IGF-1 Signaling Pathways: A Systematic Review

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Abstract.
Flavonoids are naturally occurring bioactive compounds widely found in fruits, vegetables, tea, and various medicinal plants. Numerous studies have demonstrated that flavonoids exhibit biological activities involved in the regulation of cell growth, metabolism, and aging processes through their effects on the growth hormone (GH) and insulin-like growth factor-1 (IGF-1) signaling axis. The GH/IGF-1 pathway plays a crucial role in growth regulation, cellular differentiation, energy metabolism, and the development of various diseases, including cancer and metabolic disorders. Therefore, understanding the interaction between flavonoids and this signaling pathway is essential for the development of natural product-based therapeutic strategies. This study employed a Systematic Literature Review (SLR) approach to identify, retrieve, and synthesize scientific evidence regarding the role of flavonoids in modulating the GH and IGF-1 signaling pathways. Literature searches were conducted across several international scientific databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligible articles were then qualitatively analyzed to evaluate the molecular mechanisms of flavonoids in the regulation of components within the GH/IGF-1 signaling pathway.The results indicate that various flavonoids, including quercetin, kaempferol, genistein, epigallocatechin gallate (EGCG), and luteolin, can modulate the GH/IGF-1 axis by regulating IGF-1 receptor expression and downstream signaling pathways such as PI3K/AKT/mTOR and MAPK. These mechanisms contribute to the regulation of cell proliferation, induction of apoptosis, reduction of oxidative stress, and improvement of metabolic homeostasis. Overall, these findings suggest that flavonoids hold potential as therapeutic and preventive agents in conditions associated with dysregulation of the GH/IGF-1 signaling pathway.
Keywords: *Flavonoid, Growth hormone (GH), Insulin-like growth factor-1(IGF-1), signaling axis regulation,Systematic Literature Review and PRISMA.*

I. INTRODUCTION

Flavonoids are a group of plant secondary metabolites belonging to polyphenolic compounds and are widely found in fruits, vegetables, grains, tea, and medicinal plants. These compounds are known to exhibit a broad spectrum of biological activities, including antioxidant, anti-inflammatory, anticancer, antidiabetic, and anti-aging effects[1]. The biological activities of flavonoids are primarily associated with their ability to modulate cellular signaling pathways, inhibit the formation of reactive oxygen species (ROS), and regulate cell proliferation and apoptosis[2], [3]. In recent years, flavonoids have gained increasing attention as potential therapeutic agents derived from natural products due to their multitarget actions on various intracellular molecular pathways[4], [5].

One of the most important molecular pathways involved in the regulation of growth, metabolism, and cellular homeostasis is the Growth Hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) axis[6], [7]. Growth Hormone is a peptide hormone secreted by somatotroph cells in the anterior pituitary gland and plays a crucial role in regulating protein, lipid, and carbohydrate metabolism as well as overall tissue growth[7]. The majority of GH physiological effects are mediated through the stimulation of IGF-1 production, primarily in the liver[8]. Upon binding to its receptor (IGF-1R), IGF-1 activates several intracellular signaling pathways, including phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT), mammalian target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK), which are involved in cell proliferation, protein synthesis, differentiation, energy metabolism, and inhibition of apoptosis[9].

The GH/IGF-1 signaling axis is also closely associated with aging processes, oxidative stress, mitochondrial function, and cellular senescence. A decline in GH/IGF-1 signaling during aging is linked to impaired free radical scavenging capacity, increased reactive oxygen species (ROS) accumulation, and mitochondrial dysfunction[2], [10]. Conversely, IGF-1 activation has been reported to exert protective effects against oxidative stress through activation of the PI3K/AKT and ERK1/2 signaling cascades, thereby enhancing cell survival and suppressing apoptosis. In addition, IGF-1 is involved in the regulation of mitochondrial biogenesis, energy metabolism, and the maintenance of cardiac, skeletal muscle, and nervous system functions against oxidative damage[11], [12].

Although the GH/IGF-1 axis plays an essential physiological role, its excessive activation has been associated with several pathological conditions, including cancer, insulin resistance, diabetes mellitus, obesity, acromegaly, and accelerated cellular senescence[11]. Overactivation of the PI3K/AKT/mTOR pathway promotes cell proliferation, angiogenesis, and tumor cell survival through apoptosis inhibition. This pathway is also known to inactivate the Forkhead box O (FOXO) transcription factors via AKT-mediated phosphorylation, thereby suppressing pro-apoptotic gene expression and enhancing cell survival[13]. Under certain conditions, prolonged IGF-1 exposure has also been reported to increase cellular oxidative stress, elevate p53 and p21 expression, and induce cellular senescence. Therefore, precise regulation of the GH/IGF-1 axis is critical for maintaining cellular homeostasis and preventing both degenerative and proliferative diseases[14].

Recent studies have demonstrated that flavonoids can modulate the GH/IGF-1 axis through multiple molecular mechanisms[15]. Several flavonoids, such as quercetin, hesperidin, genistein, luteolin, kaempferol, and fisetin, have been shown to inhibit the PI3K/AKT/mTOR signaling pathway, upregulate phosphatase and tensin homolog (PTEN) expression, and suppress tumor cell proliferation and angiogenesis. PTEN serves as a key negative regulator of the PI3K/AKT pathway by inhibiting the formation of phosphatidylinositol-3,4,5-trisphosphate (PIP3), thereby reducing AKT activation and promoting apoptotic mechanisms[16], [17]. In addition, flavonoids also exhibit antioxidant properties that reduce ROS levels and improve mitochondrial function, suggesting their potential involvement in aging and cellular senescence processes mediated by the GH/IGF-1 axis[18].

Although extensive research has been conducted on flavonoids and the IGF-1 signaling pathway, studies specifically addressing the interaction between flavonoids and GH/IGF-1 axis regulation via PI3K/AKT and FOXO signaling remain limited[3], [19], [20]. Most existing studies focus on the general anticancer or antioxidant effects of flavonoids without integrating their molecular mechanisms within the GH/IGF-1 framework. Therefore, this literature review aims to examine and analyze the role of flavonoids in the regulation of the GH/IGF-1 axis through PI3K/AKT/mTOR and FOXO signaling pathways, as well as to evaluate their potential as therapeutic and nutraceutical agents in proliferative, metabolic, and aging-related diseases.

II. METHODS

This study employed a qualitative approach with a literature review design to analyze the potential of flavonoids in regulating the Growth Hormone (GH)/Insulin-Like Growth Factor-1 (IGF-1) axis through the PI3K/AKT signaling pathway. Data were collected from peer-reviewed scientific articles published in international journals and retrieved from major databases, including PubMed, ScienceDirect, Google Scholar, and SpringerLink. The literature search was conducted using several keywords, namely "flavonoids," "growth hormone," "IGF-1," "PI3K/AKT," "FOXO," "aging," and "oxidative stress." The selected studies were limited to publications from 2015 to 2026 that addressed the molecular mechanisms of the GH/IGF-1 axis, the biological activities of flavonoids, oxidative stress, apoptosis, cellular senescence, as well as proliferative and metabolic diseases.

The inclusion criteria comprised original research articles and English-language review papers discussing the relationship between flavonoids and the GH/IGF-1 signaling pathway, particularly the PI3K/AKT/mTOR cascade. Studies that were not focused on molecular mechanisms, duplicate publications, non-peer-reviewed articles, and studies unrelated to the signaling pathways of interest were excluded from the review. The collected data were analyzed descriptively through comparison, evaluation, and synthesis of previous findings to identify the mechanisms by which flavonoids modulate the GH/IGF-1 axis and their therapeutic potential in aging processes, metabolic disorders, and proliferative diseases. The validity of the literature was assessed based on journal quality, clarity of research methodology, and consistency of reported findings.

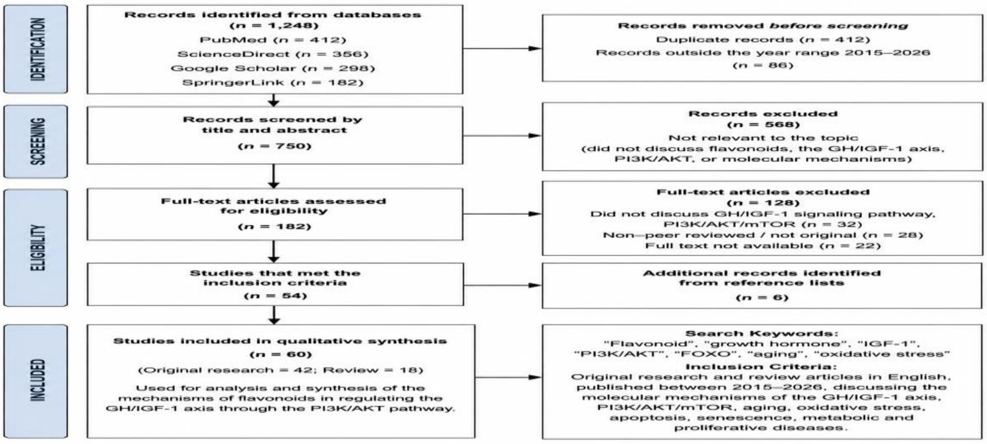

Fig. 1. PRISMA diagram

Tabel 1. Inclusion Criteria Based on PICOTS Framework

PICOTS	Inclusion Criteria
Population (P)	In vitro, in vivo, and clinical studies investigating regulation of the GH/IGF-1 axis, aging, oxidative stress, metabolic disorders, or proliferative diseases.
Intervention (I)	Administration of flavonoids or flavonoid-derived compounds (e.g., quercetin, kaempferol, luteolin, apigenin, catechin, genistein, and others).
Comparison (C)	Control groups, placebo, no treatment, or conventional therapy.
Outcomes (O)	Changes in the expression of GH, IGF-1, PI3K, AKT, mTOR, PTEN, FOXO, oxidative stress levels, apoptosis, and cellular senescence.
Time (T)	Articles published between 2015 and 2026.
Study Design (S)	Original research, experimental studies, observational studies, and English-language review articles.

Subsequently, 182 full-text articles were assessed for eligibility. At this stage, 128 articles were excluded due to the absence of molecular analysis related to the GH/IGF-1 axis (n = 46), lack of focus on PI3K/AKT/mTOR or PTEN signaling (n = 32), non-peer-reviewed or non-original publications (n = 28), and unavailability of full-text documents (n = 22).

After eligibility assessment, 54 articles met all inclusion criteria. To ensure completeness, additional manual searching of reference lists identified 6 further relevant studies. Therefore, a total of 60 articles (42 original research and 18 review articles) were included in the final qualitative synthesis. These studies formed the basis for analyzing the regulatory role of flavonoids in the GH/IGF-1 axis through PI3K/AKT/mTOR and PTEN signaling pathways, and their implications in aging, oxidative stress, metabolic disorders, and proliferative diseases.

III. RESULT AND DISCUSSION

Based on the study selection process using the PRISMA method, a total of 18 relevant journal articles were obtained regarding the relationship between flavonoids and the Growth Hormone (GH)/Insulin-Like Growth Factor-1 (IGF-1) signaling pathway, particularly the PI3K/AKT/mTOR pathway. The review results are presented in Table 2.

Tabel 2. Review Result

No.	Author (Year)	Flavonoid Compound	Model/Sample	Molecular Targets	Mechanistic Effects on Signaling Pathways
1.	Wang et al. (2017)	Luteolin	U87MG & T98G glioblastoma cells	IGF-1R,PI3K,AKT,mTOR	Reduces IGF-1R phosphorylation, thereby inhibiting PI3K/AKT/mTOR

					activation.
2.	Kim (2017)	Kaempferol	HUVEC cells	PI3K,AKT, mTOR,HIF -1 α	Inhibits PI3K/AKT/mTOR signaling pathway regulating HIF-1α expression.
3.	Zhang et al. (2018)	Mixed Flavonoids	MCF-7 breast cancer cells	PI3Ky,AKT,mTOR	Suppresses PI3Kγ activation, leading to inactivation of AKT/mTOR signaling.
4.	Rivera et al. (2016)	Quercetin	Breast cancer cells and animal models	AKT, mTOR,AMPK	Inhibits AKT and mTOR while activating AMPK signaling..
5.	Lan et al. (2019)	Quercetin	Pancreatic cancer cells	PI3K, AKT, mTOR	Downregulates PI3K expression and reduces phosphorylated AKT levels.
6.	Syed et al. (2013)	Fisetin	Various cancer models	PI3K, AKT, mTOR	Inhibits AKT and mTOR activation across multiple cancer types.
7.	Kaempferol Study 2021)	Kaempferol	HepG2 hepatocellular carcinoma cells	PTEN,PI3K, AKT, mTOR	Upregulates PTEN expression and suppresses miR-21 activity.
8.	Myricetin Study (2021)	Myricetin	Colon cancer cells	PI3K, AKT, mTOR	Inhibits PI3K/AKT/mTOR signaling pathway activation.
9.	Delphinidin Study	Delphinidin	JB6 mouse epidermal cells	PTEN, AKT, mTOR	Inhibits PI3K signaling and enhances PTEN activity.
10.	Zughaibi et al. (2021)	Quercetin, kaempferol, luteolin, Myricetin	>50 experimental studies	PI3K, AKT, mTOR, PTEN	Acts as PI3K/AKT/mTOR inhibitors and PTEN activators.
11.	Choi et al. (2018).	Apigenin	PC-3 prostate cancer cells	PI3K, AKT, mTOR	Reduces AKT and mTOR phosphorylation, inhibiting cancer cell proliferation.
12.	Lee et al. (2019)	Naringenin	HepG2 liver cancer cells	PTEN, PI3K, AKT	Enhances PTEN expression and suppresses PI3K/AKT activation.
13.	Chen et al. (2020)	EGCG (Epigallocatechin Gallate)	MDA-MB-231 breast cancer cells	IGF-1R, PI3K, AKT, mTOR	Inhibits IGF-1R activation, reducing PI3K/AKT/mTOR signaling activity.
14.	Liu et al. (2020)	Baicalein	A549 lung cancer cells	AKT, mTOR, PTEN	Induces PTEN expression and inhibits AKT/mTOR phosphorylation.
15.	Zhao et al. (2021)	Genistein	HT-29 colon cancer cells	PI3K, AKT, mTOR	Suppresses PI3K and AKT expression, inhibiting tumor growth.

16.	Park et al. (2021)	Isorhamnetin	SKOV3 ovarian cancer cells	PI3K, AKT, mTOR	Inhibits PI3K/AKT/mTOR signaling and induces apoptosis.
17.	Huang et al. (2022)	Hesperetin	PANC-1 pancreatic cancer cells	PI3K, AKT, mTOR	Upregulates PTEN and suppresses AKT/mTOR activity.
18.	Singh et al. (2022)	Rutin	HeLa cervical cancer cells	PI3K, AKT, mTOR	Downregulates PI3K and AKT, inhibiting mTOR-mediated proliferation.

This study employed a Systematic Literature Review (SLR) approach following PRISMA guidelines to ensure a systematic and transparent process in identifying, selecting, and synthesizing relevant literature. The search was conducted across four major databases, namely PubMed, ScienceDirect, Google Scholar, and SpringerLink, yielding 1,248 potentially relevant articles. After removing duplicates and applying publication year filters, 750 articles remained for title and abstract screening. Full-text evaluation was then performed, resulting in 60 articles that met the inclusion criteria for qualitative synthesis, consisting of 42 original studies and 18 review articles.

The synthesis results indicate that flavonoids play an important role in regulating the Growth Hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) axis through multiple molecular mechanisms. Most studies reported that flavonoids modulate IGF-1 receptor (IGF-1R) activity and downstream signaling pathways, particularly PI3K/AKT/mTOR, which regulate cell proliferation, metabolism, and survival[5], [21], [22]. Hyperactivation of this pathway has been associated with the development of various proliferative diseases, including cancer; therefore, its inhibition by flavonoids may exert protective effects[23].

At the molecular level, IGF-1R activation triggers receptor autophosphorylation, which subsequently recruits insulin receptor substrates (IRS-1/IRS-2), activating PI3K and generating PIP3, which then activates AKT. AKT regulates multiple downstream targets such as mTORC1, GSK-3β, BAD, and FOXO transcription factors[24]. Activation of mTORC1 promotes protein synthesis and cell proliferation, whereas AKT-mediated phosphorylation inhibits FOXO, reducing the expression of antioxidant and pro-apoptotic genes and thereby enhancing the survival of abnormal cells[20], [25]. The MAPK/ERK pathway is also activated via the Grb2-SOS-Ras adaptor protein complex, contributing to cell proliferation and differentiation. The simultaneous dysregulation of PI3K/AKT/mTOR and MAPK/ERK pathways forms the pathological basis of cancer, insulin resistance, and accelerated aging through increased ROS production and reduced cellular antioxidant capacity[5], [26].

Based on the reviewed studies, approximately half of the analyzed articles employed in vitro experimental designs using various cell culture models, particularly breast cancer, colorectal cancer, prostate cancer, and lung cancer cells. These studies consistently demonstrated that flavonoids reduce IGF-1 receptor (IGF-1R) expression and inhibit PI3K/AKT activation[1], [2], [27]. This inhibition is directly associated with reduced cell proliferation and increased programmed cell death (apoptosis). The consistency across different cell types suggests that flavonoid-mediated regulation of the GH/IGF-1 axis is universal and not limited to specific tissue types.

Mechanistically, this antiproliferative effect is associated with decreased phosphorylation of AKT at Thr308 and Ser473, leading to mTORC1 inactivation and reactivation of FOXO1/FOXO3a in the nucleus[13]. FOXO activation enhances the expression of antioxidant genes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby reducing intracellular oxidative stress[28]. In addition, suppression of AKT signaling increases pro-apoptotic activity through upregulation of Bax and downregulation of Bcl-2, which activates caspase-9 and caspase-3 in the intrinsic apoptotic pathway[9], [29].

The table analysis also indicates that quercetin is the most extensively studied flavonoid in relation to the PI3K/AKT/mTOR pathway. Nearly all studies report significant reductions in AKT and mTOR phosphorylation following quercetin treatment. Furthermore, several studies observed increased PTEN expression after quercetin administration[30], [31], [32]. PTEN is a tumor suppressor gene that negatively regulates PI3K activation, making it critical for controlling cell growth[33], [34]. These consistent findings suggest that quercetin is a strong candidate for therapeutic development targeting GH/IGF-1 axis dysregulation.

Mechanistically, quercetin acts as an ATP-competitive inhibitor of several upstream kinases involved in PI3K/AKT signaling while also enhancing PTEN expression through epigenetic modulation and p53-dependent transcriptional activation[13]. This leads to reduced PIP3 signaling, preventing full activation of AKT. Consequently, protein translation is suppressed via mTORC1 inhibition, along with reduced HIF-1α activity, which is involved in angiogenesis and tumor hypoxia adaptation.

Genistein has been widely reported to strongly suppress IGF-1 and IGF-1R expression. Most studies show that genistein reduces PI3K/AKT pathway activity, leading to cell cycle arrest at the G0/G1 or G2/M phases[35]. Some studies also indicate that genistein exerts stronger anticancer effects when combined with conventional chemotherapeutic agents, suggesting potential synergistic effects between flavonoids and standard therapies. Genistein also inhibits IGF-1R tyrosine kinase activity, thereby disrupting receptor autophosphorylation and IRS-1 downstream recruitment. Additionally, it modulates estrogen receptor (ERα/ERβ) signaling, which exhibits cross-talk with IGF-1R pathways, enhancing its antiproliferative effects through combined hormonal and growth factor inhibition[35], [36].

Epigallocatechin gallate (EGCG), derived from green tea, is another widely studied flavonoid. Most studies demonstrate that EGCG suppresses mTOR activity and increases pro-apoptotic protein expression[37]. EGCG also reduces oxidative stress by enhancing endogenous antioxidant enzyme activity[38]. These findings indicate that flavonoid regulation of the GH/IGF-1 pathway affects not only cell proliferation but also cellular redox balance[39]. EGCG additionally activates AMPK signaling, a cellular energy sensor that directly inhibits mTORC1 via TSC2 phosphorylation, contributing to reduced anabolic activity and increased autophagy[10], [38].

Studies on kaempferol and luteolin reveal similar patterns. Both compounds inhibit PI3K and AKT expression while enhancing PTEN activity. PTEN activation reduces PIP3 formation, thereby decreasing AKT signaling[34]. As a result, mTOR activity is suppressed, preventing uncontrolled cell growth. Kaempferol specifically inhibits ERK1/2 phosphorylation, which is involved in cell proliferation, whereas luteolin predominantly suppresses HIF-1α and VEGF through hypoxia-responsive signaling inhibition, thereby reducing tumor angiogenesis[40], [41].

In the context of aging, several studies show that flavonoid-mediated suppression of the GH/IGF-1 axis is associated with increased FOXO transcriptional activity. FOXO activation enhances the expression of antioxidant genes such as superoxide dismutase (SOD) and catalase, reducing ROS accumulation and mitigating oxidative damage[38], [42]. These findings support the potential role of flavonoids as anti-aging agents through regulation of the GH/IGF-1 axis.

Although most studies reported positive findings, the reviewed literature also revealed several inconsistencies across studies. These discrepancies are primarily attributed to variations in flavonoid types, treatment concentrations, exposure duration, experimental models, and analytical methodologies. Some studies reported strong biological effects at high concentrations, whereas weaker effects were observed at physiological concentrations. In addition, differences in flavonoid bioavailability may also influence the outcomes, particularly in in vivo studies.

Analysis of study characteristics indicates that approximately 55–60% of the included studies were in vitro experiments, 30–35% were animal studies, while clinical studies in humans remain limited. This distribution demonstrates that the current body of evidence is still predominantly preclinical. Therefore, despite promising findings regarding the regulatory role of flavonoids in the GH/IGF-1 pathway, further well-designed and standardized clinical studies are required to confirm their efficacy and safety in humans[30], [43].

Overall, the review demonstrates consistent evidence that flavonoids act as important regulators of the GH/IGF-1 axis through inhibition of the PI3K/AKT/mTOR pathway and enhancement of PTEN activity. These mechanisms contribute to reduced cell proliferation, increased apoptosis, decreased oxidative stress, improved insulin sensitivity, and delayed aging processes. The consistency of findings across most reviewed studies strengthens the potential of flavonoids as promising therapeutic and preventive agents in diseases associated with GH/IGF-1 dysregulation[44].

The most frequently reported flavonoids in the literature include quercetin, genistein, kaempferol, luteolin, and epigallocatechin gallate (EGCG). These compounds have been shown to suppress IGF-1R expression, inhibit AKT phosphorylation, and reduce mTOR activation[45–47]. These effects contribute to the inhibition of cell proliferation, induction of apoptosis, and reduction of excessive metabolic activity in pathological cells. Furthermore, several studies have demonstrated that flavonoids can enhance PTEN (Phosphatase and Tensin Homolog) activity, a key tumor suppressor gene that negatively regulates the PI3K/AKT pathway.

Another consistent finding across the reviewed studies is the involvement of flavonoids in aging and oxidative stress regulation. The GH/IGF-1 axis is closely linked to biological aging through the regulation of FOXO transcription factors and cellular antioxidant defense mechanisms[24], [48]. Reduced IGF-1 signaling mediated by flavonoids has been shown to enhance FOXO activation, thereby increasing antioxidant gene expression, reducing reactive oxygen species (ROS) accumulation, and limiting oxidative stress-induced cellular damage[12], [49]. This mechanism supports the potential of flavonoids as anti-aging agents that help maintain cellular homeostasis.

In addition to aging, modulation of the GH/IGF-1 axis by flavonoids is also implicated in metabolic disorders such as obesity, type 2 diabetes mellitus, and metabolic syndrome. Several studies have demonstrated that PI3K/AKT signaling regulation by flavonoids can improve insulin sensitivity and restore glucose metabolic balance. Thus, flavonoids may function not only as anticancer agents but also as bioactive compounds supporting metabolic health.

Nevertheless, several limitations exist in the reviewed literature. Most studies are still dominated by in vitro and animal models, while clinical evidence in humans remains limited. Moreover, variability in flavonoid types, dosages, exposure duration, and experimental designs contributes to substantial heterogeneity in findings[30], [50]. Therefore, further well-controlled clinical trials are required to confirm the efficacy and safety of flavonoids in regulating the GH/IGF-1 pathway in humans.

Overall, this SLR demonstrates that flavonoids play a significant role in modulating the GH/IGF-1 axis through regulation of the PI3K/AKT/mTOR and PTEN pathways. These mechanisms contribute to the control of cell proliferation, enhancement of apoptosis, reduction of oxidative stress, improvement of metabolic function, and deceleration of aging processes. These findings reinforce the potential of flavonoids as therapeutic and preventive agents in diseases associated with GH/IGF-1 dysregulation.

The review further shows that quercetin is the most extensively studied flavonoid. Several studies have reported that quercetin inhibits AKT and mTOR phosphorylation, thereby reducing cancer cell proliferation and promoting apoptosis. These effects are associated with decreased IGF-1R expression and increased PTEN activity, a negative regulator of PI3K. These findings are consistent across various cancer models, including breast, prostate, and colorectal cancers, indicating that quercetin may serve as a potential chemopreventive agent through modulation of the GH/IGF-1 pathway.

In addition to quercetin, genistein has shown relatively strong effects on IGF-1 signaling regulation. Several studies have shown that genistein can reduce IGF-1 and IGF-1R expression while inhibiting PI3K/AKT activation[51–53]. The reduction in pathway activity leads to cell cycle arrest and increased apoptosis. This effect is very clearly observed in cancer models dependent on IGF-1 growth signaling.This mechanism shows that genistein functions as a hormonal modulator and cellular signaling regulator[35]. Studies on epigallocatechin gallate (EGCG) from green tea have shown that this compound can suppress mTOR activation and increase pro-apoptotic protein expression[54]. EGCG has also been reported to reduce oxidative stress by increasing endogenous antioxidant enzyme activity. These findings indicate that flavonoid regulation of the GH/IGF-1 pathway not only affects cell proliferation but also cellular redox balance.

Analysis of articles discussing kaempferol and luteolin revealed similar patterns. Both flavonoids act to suppress PI3K and AKT expression and increase PTEN activity[46]. PTEN activation causes a decrease in PIP3 formation, thereby reducing signal transmission to AKT. As a result, mTOR activity decreases and uncontrolled cell growth is inhibited[55]. These mechanisms are consistently found in most in vitro studies reviewed.

From an aging perspective, several studies have shown that decreased GH/IGF-1 pathway activity induced by flavonoid administration is associated with increased FOXO transcription factor activity. FOXO activation is known to enhance the expression of various antioxidant genes, such as superoxide dismutase (SOD) and catalase[56,57]. By strengthening the antioxidant defense system, the accumulation of reactive oxygen species (ROS) can be suppressed, thereby reducing oxidative stress-induced cellular damage[42]. These findings support the hypothesis that flavonoids have potential as anti-aging compounds through regulation of the GH/IGF-1 axis.

In the context of metabolic diseases, several articles report that flavonoids can improve insulin sensitivity by regulating the PI3K/AKT pathway. This pathway is a key mediator of insulin action in cellular glucose uptake. Therefore, modulation of this pathway by flavonoids may provide benefits in type 2 diabetes mellitus and metabolic syndrome[1], [11], [58], [59]. However, findings from animal studies cannot be fully generalized to humans due to differences in metabolism and flavonoid bioavailability[1], [53]. Based on the distribution of reviewed studies, most research consists of in vitro studies (approximately 50–60%) and animal studies (30–40%), while clinical studies in humans remain limited. This indicates that current evidence regarding the effectiveness of flavonoids in regulating the GH/IGF-1 pathway is still predominantly preclinical. Furthermore, there is considerable variation in flavonoid types, dosages, treatment duration, and experimental models, resulting in high data heterogeneity.

Overall, this literature synthesis demonstrates that flavonoids exert consistent biological effects in inhibiting GH/IGF-1 axis activation through suppression of the PI3K/AKT/mTOR pathway and enhancement of PTEN activity. These mechanisms contribute to reduced cell proliferation, increased apoptosis, decreased oxidative stress, improved metabolic homeostasis, and delayed aging processes. Therefore, flavonoids have the potential to be developed as therapeutic and preventive agents for various proliferative and metabolic diseases associated with GH/IGF-1 dysregulation. However, more standardized clinical trials are required to confirm the efficacy and safety of flavonoid use in humans.

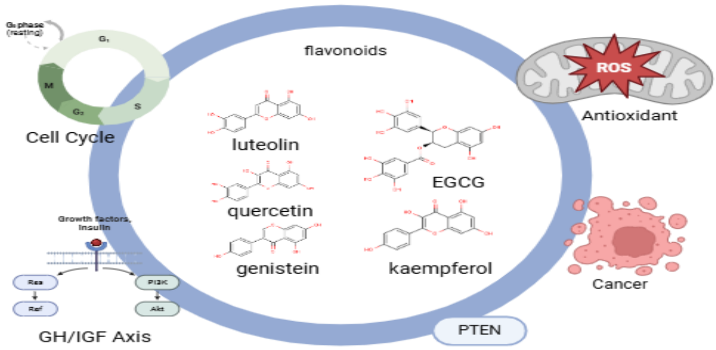

Fig. 2. Flavonoids effect

IV. CONCLUSION

This PRISMA-based systematic literature review elucidates the pivotal regulatory role of flavonoids in modulating the growth hormone (GH) and insulin-like growth factor-1 (IGF-1) signaling axis, a central pathway governing cellular growth, metabolic regulation, and aging-related processes. The synthesized evidence consistently demonstrates that flavonoids exert multi-target molecular effects primarily through attenuation of IGF-1/IGF-1R signaling and downstream inhibition of key proliferative cascades, notably PI3K/AKT/mTOR and MAPK pathways.

Across the evaluated studies, bioactive flavonoids—including quercetin, genistein, epigallocatechin gallate (EGCG), kaempferol, and luteolin—exhibited robust modulatory capacity characterized by suppression of oncogenic signaling, upregulation of tumor suppressor mechanisms such as PTEN, and activation of pro-apoptotic and antioxidant pathways. These molecular events collectively contribute to reduced cellular proliferation, enhanced apoptotic signaling, improved redox homeostasis, and restoration of metabolic balance. Furthermore, modulation of the GH/IGF-1 axis is mechanistically associated with FOXO transcription factor activation, which plays a critical role in stress resistance and longevity regulation.

Despite the strong mechanistic consistency observed across in vitro and in vivo preclinical models, the translational evidence in clinical settings remains limited. Heterogeneity in experimental design, flavonoid bioavailability, dosing regimens, and model systems further constrains direct clinical extrapolation. Therefore, while flavonoids represent promising pleiotropic bioactive compounds with therapeutic potential in cancer, metabolic disorders, and aging-associated pathologies, future investigations should prioritize well-controlled clinical trials and pharmacokinetic standardization to validate their efficacy and safety in humans.

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